VOLUME 42 NUMBER 4

ARCHIVES OF

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OCTOBER 1949

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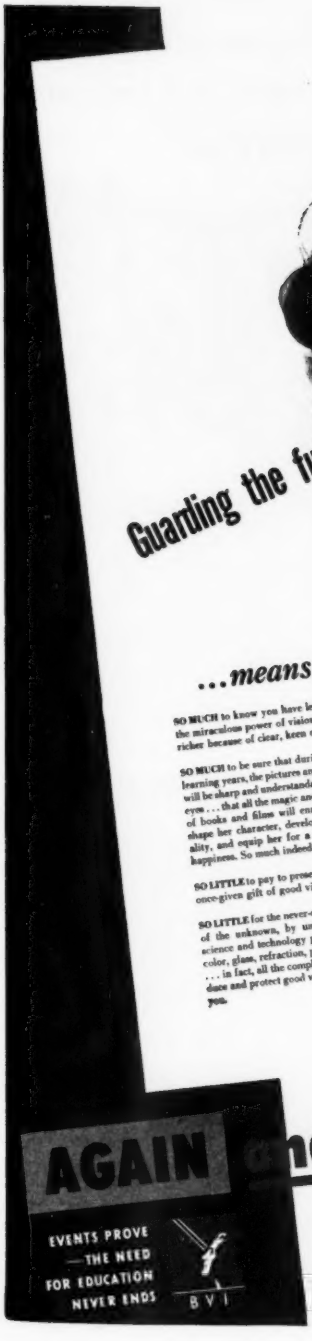

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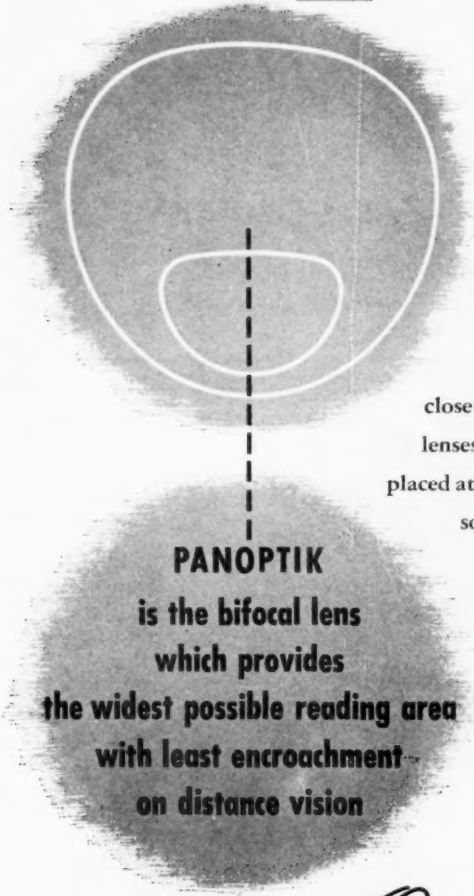

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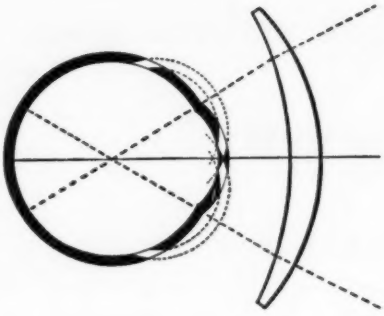

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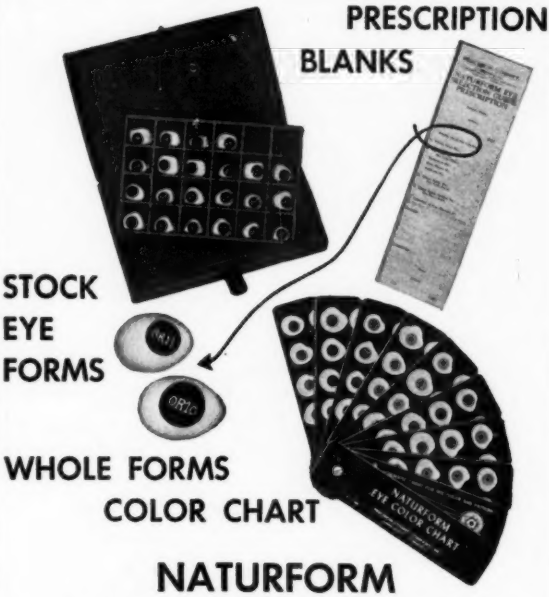

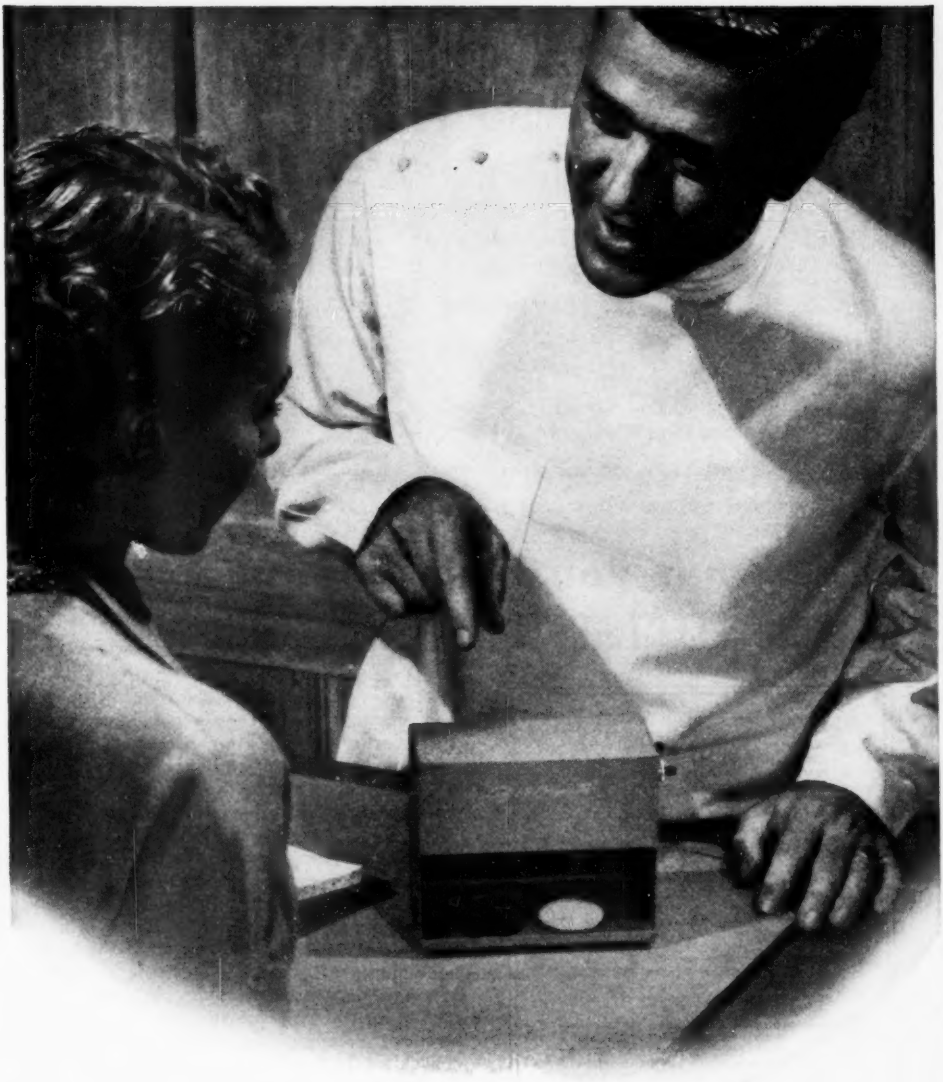

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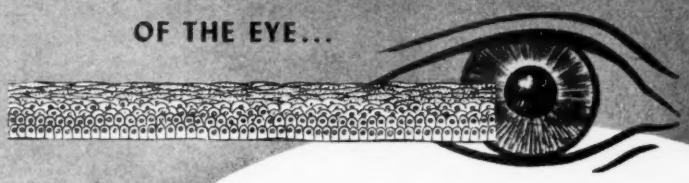

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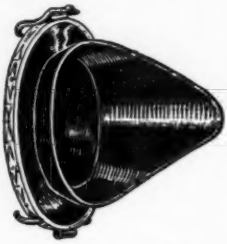

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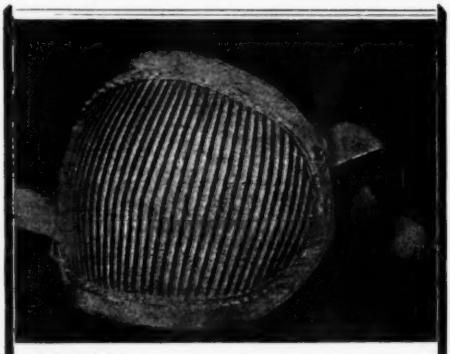

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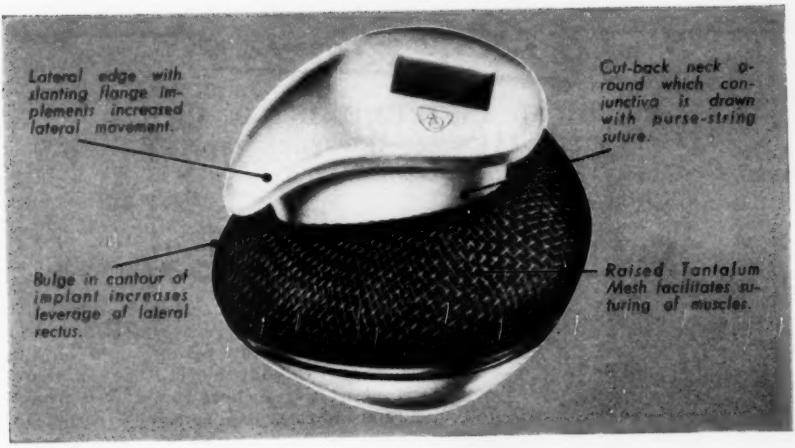
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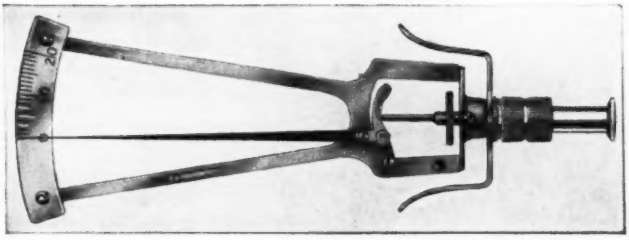

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ARCHIVES OF OPHTHALMOLOGY

VOLUME 42 OCTOBER 1949 NUMBER 4

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ANEURYSM OF THE POSTERIOR COMMUNICATING ARTERY

BERNARD J. ALPERS, M.D.
AND
N. S. SCHLEZINGER, M.D.
PHILADELPHIA

THE growing interest in the clinical recognition of cerebral aneurysms, due largely to the promising possibilities of surgical treatment, demands elucidation of their characteristics for purposes of accurate diagnosis. For this reason we report a group of cases of aneurysm of the posterior communicating artery, in order to call attention to salient features for diagnosis, as well as to indicate the possibilities of treatment.

REPORT OF CASES

CASE 1.—*History.*—C. S., a married man aged 59, a railroad car inspector, was admitted to the neurologic service of the Jefferson Hospital on April 18, 1947 with a history of having had the onset of right frontal headache seventeen days before admission. The headache was constant and was associated with buzzing in the head, ringing in the ears, impairment of vision and intermittent nausea. The headache gradually became more pronounced and ten days after onset was followed by vomiting and sudden severe pain behind the right eye and in the back of the neck. The pain persisted and was soon followed by drooping of the right eyelid. When the right eyelid was raised double vision was noted. The symptoms persisted until the patient's admission to the hospital.

The past medical history revealed that the patient had had typhoid in childhood and influenza in 1918. The family history revealed that the mother had had hemiplegia before her death, at the age of 84.

Examination.—General physical examination disclosed no abnormalities of the heart, lungs or abdomen. The blood pressure was 170 systolic and 90 diastolic.

Neurologic examination revealed ptosis of the right eyelid; right internal ophthalmoplegia and paralysis of upward, inward and downward gaze of the right eye; slightly faster patellar and achilles reflexes on the left, and slight nuchal rigidity.

Laboratory Data.—Urine was normal. Blood studies revealed 81 per cent hemoglobin, 4,600,00 red cells and 11,400 white cells. The Wassermann and Kahn reactions of the blood were negative. The urea clearance was 80 per cent. Studies of the spinal fluid revealed xanthochromia, a pressure of 150 mm., a negative Wassermann reaction and a total protein content of 70 mg. per hundred cubic centimeters. The electrocardiogram revealed a low voltage T wave in the limb leads, suggesting myocardial change. A roentgenogram of the chest showed cardiac enlargement, and a roentgenogram of the skull revealed no abnormality.

From the Department of Neurology, Jefferson Medical College.

Comment.—The history of onset with headache followed several days later by right oculomotor paralysis was so characteristic that a diagnosis of aneurysm of the right posterior communicating artery was made and craniotomy performed on May 5, 1947 by Dr. Rudolph Jaeger, without benefit of an arteriogram. An aneurysm of the right posterior communicating artery was disclosed and removed. Death occurred shortly after operation.

Case 2.—*History.*—D. B., a white housewife aged 29, was first admitted to the neurologic service of the Jefferson Hospital on Dec. 10, 1946 and was subsequently readmitted on Jan. 15, 1947. The onset of the present illness occurred three weeks prior to admission to the hospital, when the patient felt a dull pain in and above the right eye. One week later she experienced a sudden sharp pain in the right side of her head, lasting only a few seconds, but within a few days severe, sharp pain reappeared behind the right eye and involved the entire right side of the head and face. The pain remained severe for two days and extended to involve the entire head, as well as the neck, arms and legs. As it subsided somewhat, drooping of the right eyelid appeared and was accompanied with double vision. The drooping of the eyelid increased rapidly to complete closure of the eye, which persisted, while the pain gradually diminished.

Examination.—General physical examination revealed no abnormalities of the heart, lungs or abdomen. The blood pressure was 130 systolic and 84 diastolic. Neurologic examination revealed a relatively larger pupil on the right side, which reacted sluggishly to light and in accommodation; almost complete ptosis of the right eyelid; marked impairment of upward, inward and downward gaze of the right eye, and a relatively diminished right corneal reflex.

Laboratory Data.—The urine was normal. Blood studies revealed 75 per cent hemoglobin, 3,800,000 red cells and 9,200 white cells. The Wassermann and Kahn reactions of the blood were negative. Spinal fluid studies revealed a clear and colorless fluid, with red blood cells observed on microscopic examination. The spinal fluid pressure was 200 mm., and the Wassermann reaction was negative. A roentgenogram of the skull showed no abnormalities. A cerebral arteriogram of the right internal carotid artery showed no evidence of an intracranial aneurysm (fig. 1).

Comment.—In view of the characteristic onset and course of the illness, a presumptive diagnosis of intracranial aneurysm involving either the right internal carotid artery or the right posterior communicating artery was made, despite the normal arteriogram. Craniotomy was performed on January 20 by Dr. Rudolph Jaeger, and a saccular aneurysm originating from the right posterior communicating artery was revealed. Although the aneurysm ruptured on removal, it was extirpated completely after proximal and distal ligation. Prior to operation there had been definite evidence of improvement of function of the right oculomotor nerve, as shown by diminished ptosis and increased movement of the eye. After operation there was a recurrence of paralysis of the right oculomotor nerve. Recovery was uneventful except for this, and the patient was discharged on February 12.

Case 3.—*History.*—N. T., a Negro woman aged 36, was referred from the Wills Hospital to the neurologic service of the Jefferson Hospital on Oct. 16, 1946. The onset of the present illness occurred on August 30, six weeks before her admission, when the patient had a lower tooth extracted on the right side. Five days later, while on her way to work, she suddenly experienced a severe headache in the region of the vertex, with extension into the back of the neck. The headache persisted for a week, was partially relieved by medication and was increased by movement of the head. As the headache gradually subsided, it was replaced by

a dull pain in and around the left eye; this pain persisted and was followed within a day or two by drooping of the left eyelid. The ptosis increased rapidly within two days to the point of complete closure of the left eye. The drooping of the left eyelid persisted, but the pain in the left eye subsided gradually over a period of about two weeks. The family and past medical histories were not pertinent to her present problem.

Examination.—General physical examination revealed no abnormalities of the heart, lungs or abdomen. The blood pressure was 110 systolic and 60 diastolic.

Neurologic examination revealed the following significant changes: a relatively larger pupil on the left side, which failed to react to light or in accommodation; almost complete ptosis of the left eyelid; external strabismus of the left eye with inability to move the left eye upward, inward and downward except for slight

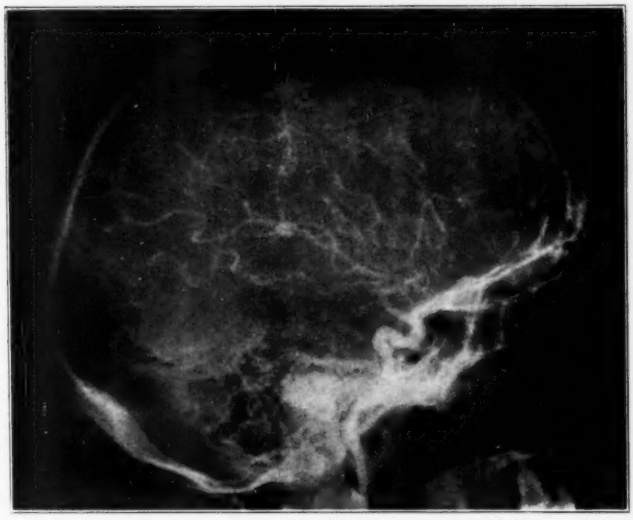

Fig. 1 (case 2).—Normal arteriogram in a proved case of aneurysm of the posterior communicating artery.

counterclockwise rotary movement on attempted downward gaze; equally active corneal reflexes, and no disturbance of sensation over the face.

Laboratory Data.—Urine was normal. Blood studies revealed 78 per cent hemoglobin, 4,100,000 red cells and 6,000 white cells. The Wassermann and Kahn reactions of the blood were negative. Spinal fluid studies revealed a clear and colorless fluid, under 95 mm. of pressure, 1 cell per cubic millimeter, a negative Wassermann reaction and a colloidal gold curve of 0000000000. The electrocardiogram was normal. Roentgenograms of the chest and the skull showed no abnormalities. A cerebral arteriogram of the left internal carotid artery was suggestive of a small aneurysm of the left posterior communicating artery (fig. 2).

Comment.—Because of the characteristic history and the evidence of a progressive paralysis of the left oculomotor nerve, as well as possible involvement of

the left trochlear nerve, a presumptive diagnosis of intracranial aneurysm originating either from the left posterior communicating artery or from the left internal carotid artery was made. A craniotomy was performed on Dec. 4, 1946 by Dr. Rudolph Jaeger, and a small saccular aneurysm was discovered attached to the left posterior communicating artery. Proximal ligation and obliteration of the aneurysm were carried out, after which the patient made an uneventful recovery. Both at the time of discharge, on December 15, and on subsequent observation no evidence of recovery of function of the left oculomotor nerve was disclosed.

Case 4.—*History.*—M. B., a Negro woman aged 34, was referred from the Wills Hospital to the neurologic service of the Jefferson Hospital on June 17, 1946 with a history of having had occasional pain beneath the left eye for three or four years. The pain was considered to be neuralgia and was relieved by acetylsalicylic acid. One month before admission the patient was awakened

Fig. 2 (case 3).—Arteriogram demonstrating aneurysm of the left posterior communicating artery.

during the night by a severe pain in the left occipital region, the pain extending forward over the left side of the head into the left eye. The severe pain persisted for three days and subsided gradually over a period of three weeks, a process which was associated with drooping of the left eyelid and double vision. The drooping of the eyelid increased to the point of complete closure after three days. The family and past medical histories were without significance.

General physical examination revealed no abnormalities of the heart, lungs and abdomen. The blood pressure was 110 systolic and 70 diastolic.

Neurologic examination revealed the following significant changes: a relatively larger pupil on the left, with both pupils reacting well to light and in accommodation; almost complete ptosis of the left eyelid; slight external strabismus of the left eye and marked limitation of movement of the left eye upward, inward and

downward; equally active corneal reflexes, and no disturbance of sensation over the face.

Laboratory Data.—The urine was normal. Blood studies revealed 71 per cent hemoglobin, 4,200,000 red cells and 9,600 white cells. The Wassermann and Kahn reactions of the blood were negative. The spinal fluid was clear and colorless, with a pressure of 120 mm.; studies revealed less than 1 cell per cubic millimeter, a negative Wassermann reaction and a colloidal gold curve of 0001221000. A roentgenogram of the skull showed no abnormalities (fig. 3).

Comment.—On the basis of the characteristic onset and course of the illness, as well as the evidence of ophthalmoplegia in the distribution of the left oculomotor, and possibly the left trochlear, nerves, a presumptive diagnosis of intracranial aneurysm involving either the left internal carotid artery or the left posterior communicating artery was made. A craniotomy was performed on July 3, 1946 by Dr. Rudolph Jaeger, and a small saccular aneurysm was revealed, taking its

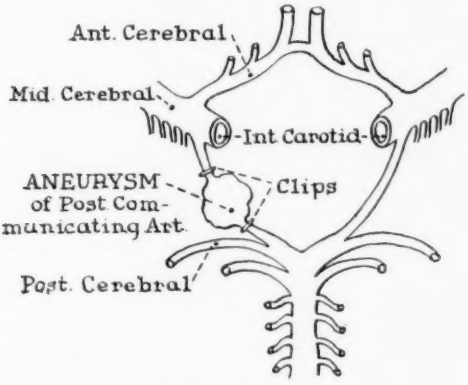

Fig. 3 (case 4).—Aneurysm of the left posterior communicating artery, shown in diagram.

origin from the left posterior communicating artery. The aneurysm was removed after proximal and distal ligation. The operation was followed by persistence of the complete paralysis of the left oculomotor nerve which was still present when the patient was discharged on July 16. Subsequently, there was progressive return of function of the left oculomotor nerve, and after several months no evidence of weakness of the extraocular muscles could longer be detected.

CASE 5.—*History.*—C. F. M., a woman aged 43, a telephone operator, was admitted to the medical service of the Jefferson Hospital on May 23, 1946. The onset of the present illness occurred suddenly at about 1 a. m., five days before admission, when the patient awoke from her sleep with a headache. She was able to fall back to sleep, but four hours later she again awoke with a severe headache, which was generalized and dull in character. The headache persisted and on the day of admission became much more pronounced during the afternoon. At that time there was also noted sharp, lancinating pain in the right eye, associated with bright flashes of light in the visual field of that eye. Within a half-hour other

symptoms developed in the form of generalized weakness, perspiration, nausea, vomiting and pain the back. The past medical history revealed that the patient had had a chronic infection of the ear, with intermittent drainage affecting both ears, for fifteen years, with resultant impairment of hearing. The family history was without significance.

Examination.—General physical examination showed no abnormalities of the heart, lungs or abdomen. The blood pressure was 110 systolic and 70 diastolic. Examination of the ears showed chronic otitis media bilaterally.

Neurologic examination revealed nuchal rigidity, a bilateral Kernig sign and slight weakness of upward and inward gaze of the right eye. Within a few days the weakness of the extraocular muscles of the right eye progressed to the point of complete paralysis of the right oculomotor nerve, including ptosis and a dilated pupil, which failed to react to light or in accommodation. Subsequently, over a period of about two weeks, there was diminution in ptosis of the right eye, and the right pupil, although still dilated, showed a reaction to light and in accommodation. The headaches persisted. Craniotomy was performed on June 17 (fig. 4).

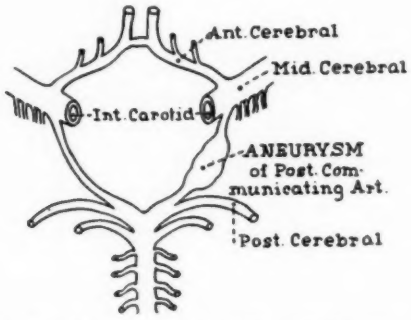

Fig. 4 (case 5).—Aneurysm of the right posterior communicating artery, shown in diagram.

Laboratory Data.—The urine was normal. Blood studies revealed 84 per cent hemoglobin, 4,160,000 red cells and 9,950 white cells. The Wassermann and Kahn reactions of the blood were negative. The spinal fluid was under increased pressure of 215 mm. and was grossly bloody. A roentgenogram of the skull was normal except for evidence of mastoid infection bilaterally.

Comment.—Craniotomy revealed a saccular aneurysm of the right posterior communicating artery at the edge of the tentorium with discoloration of the surrounding dura. During the operation the aneurysm, which was about 1 cm. in diameter, ruptured but was ultimately removed after proximal and distal ligation. Immediately after operation the patient had left hemiplegia, as well as complete paralysis of the right oculomotor nerve. The hemiplegia subsided, but the right oculomotor nerve palsy was still present at the time of discharge, on July 16, 1946.

CASE 6.—*History.*—A. L. R., a Negro woman aged 60, was referred from the Wills Hospital to the neurologic service of the Jefferson Hospital on Feb. 24, 1946, with a history of having awakened one morning seven weeks before admission

to discover slight drooping of her left eyelid. Within a few hours the drooping of the eyelid had increased to the point of complete closure of the eye. At no time did she experience headache or any other symptoms referable to the nervous system. The family and past medical histories were noncontributory.

Examination.—General physical examination revealed a functional systolic murmur but no other abnormalities of the heart, lungs or abdomen. The blood pressure was 130 systolic and 70 diastolic.

Neurologic examination revealed the following significant changes: retinal choroiditis bilaterally with some narrowing and increased tortuosity of the smaller retinal arterioles; a dilated left pupil, which failed to react to light or in accommodation, and a smaller right pupil, which reacted well to light and in accommodation; complete ptosis of the left eyelid; external strabismus of the left eye with inability

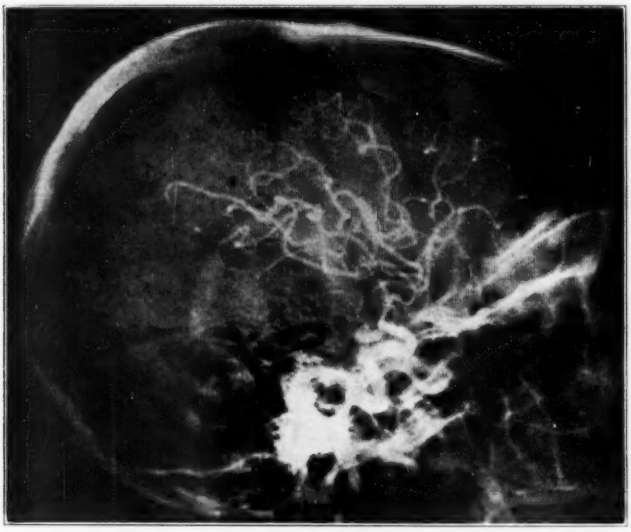

Fig. 5 (case 6).—Normal arteriogram in a case of aneurysm of the posterior communicating artery.

to move the left eye upward, inward and downward, and equally active corneal reflexes.

Laboratory Data.—The urine was normal. Blood studies revealed 58 per cent hemoglobin, 3,100,000 red cells and 5,600 white cells. The Wassermann and Kahn reactions of the blood were negative. The blood urea nitrogen was 9.8 mg. and the blood sugar 80 mg. per hundred cubic centimeters. The protein level of the spinal fluid was 58 mg. per hundred cubic centimeters, but the fluid was otherwise normal. The electrocardiogram showed a left axis deviation but no other abnormalities. A roentgenogram of the chest showed some widening of the aortic arch. A roentgenogram of the skull was normal. Cerebral arteriography revealed no evidence of an intracranial aneurysm (fig. 5).

Comment.—In view of the course of illness, which was characterized by the sudden onset of partial paralysis of the left oculomotor nerve and possibly involvement of the left trochlear nerve, a presumptive diagnosis of an intracranial aneurysm involving either the left internal carotid artery or the left posterior communicating artery was made, despite the absence of headache and the normal appearance of the arteriogram. A craniotomy was performed on March 27, 1946 by Dr. Rudolph Jaeger, and a saccular aneurysm was disclosed originating in the left posterior communicating artery near its junction with the left internal carotid artery. It was impossible to remove the aneurysm successfully, and treatment was limited to both intracranial and cervical ligation of the left internal carotid artery. Death occurred three days after operation. Autopsy was not allowed.

Fig. 6.—Aneurysm of the right posterior communicating artery and a small aneurysm of the right middle cerebral artery.

CASE 7.—*History.*—M. R., a white woman aged 58, was admitted to the neurologic service of the Jefferson Hospital on Sept. 21, 1947. For many years she had suffered from headaches confined to the right side of the head, which occurred at intervals of two to four weeks and were associated with nausea and vomiting. These attacks had been regarded as typical migraine headaches and, indeed, appeared to have all the features of such headaches. Two weeks before admission to the hospital she experienced sudden, persistent pain behind the right eyeball. She had no further symptoms except for the constant retro-orbital pain on the right side, which defied relief. One week after its appearance she suddenly experienced a "bursting sensation" in her head during a trying telephone conversation held in her capacity as secretary to a physician. The headache was intense and was followed by slight

drooping of the right eyelid and diplopia. With the persistent and constant headache there developed in the course of twenty-four hours complete ptosis of the right eyelid and inability to rotate the right eyeball, associated with diplopia. At this time she entered the hospital for study.

Neurologic Examination.—The patient was profoundly prostrated. Examination revealed pronounced nuchal stiffness and a bilateral Kernig sign; complete ptosis of the right eyelid with inability to rotate the right eyeball upward, inward or downward, and a grossly bloody spinal fluid.

Laboratory Data.—The urine was normal. Blood count showed 3,940,000 red cells, 8,200 white cells and 71 per cent hemoglobin. The blood urea nitrogen was 22.8 mg. per hundred cubic centimeters and the urea clearance 140 per cent. The Wassermann and Kahn reactions of the blood were negative. The spinal fluid was clear, with a pressure of 130 mm., protein content of 25 mg. per hundred cubic centimeters, 3 cells per cubic millimeter, a negative Wassermann reaction and a normal colloidal gold curve. The electrocardiogram revealed a mild left axis deviation but was otherwise normal. A roentgenogram of the skull revealed no abnormalities.

Comment.—This case reveals several pertinent problems associated with the problem of aneurysm. The long-standing history of hemicrania suggestive of migraine is not infrequently encountered in any extensive experience with aneurysm. The development of the illness, leading to hospitalization, was characteristic of a ruptured aneurysm and was associated with intense headache, signs of meningeal irritation and cranial nerve palsy. Finally, the problem of treatment was well illustrated by this case. Because of the clear evidence of rupture and subarachnoid hemorrhage and the indications of profound prostration, operation was not undertaken. The patient died shortly after entering the hospital, and autopsy revealed a ruptured aneurysm of the right posterior communicating artery and an unruptured small aneurysm of the right middle cerebral artery (fig. 6).

GENERAL COMMENT

Incidence.—Aneurysms involving the posterior communicating artery are said to be rare, but the present series of 7 verified cases indicates that they are not as rare as they seem. Dandy [1] was unable to discover a single case in his series of 133 verified aneurysms. He explained the disparity between his observations and those of others by the fact that careful dissection of the aneurysms indicated that they actually arose from the internal carotid artery. Our observations demonstrate that aneurysms may involve the posterior communicatnig artery alone, without taking origin from the internal carotid artery. Of 1,025 verified cases of aneurysms from the literature, McDonald

1. Dandy, W.: Intracranial Arterial Aneurysm, Ithaca, N. Y., Comstock Publishing Company, Inc., 1945.

and Korb [2] found the posterior communicating artery involved in 66. Aneurysms of this artery were reported by Gall [3] who found 4 in a series of 62 aneurysms; by Lebert [4] who found 7 among 86 aneurysms; by Epron,[5] who reported 4 in a series of 89 aneurysms, and by Hey,[6] Reinhardt,[7] Symonds,[8] Berger [9] (2 cases), Hassin,[10] Shore,[11] Schmidt [12] (2 cases), Sands,[13] Dassen,[14] Kersley,[15] Krayenbühl,[16] Fattovich,[17] Keegan and Bennett,[18] Strauss, Globus and Ginsburg,[19] Dial and Maurer,[20] Frazier [21] and Elmer and Baylon.[22]

Clinical Features.—The clinical features of aneurysm of the posterior communicating artery are similar to those of aneurysm involving other

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portions of the circle of Willis. The typical instance is characterized by headache, usually unilateral and often recurrent, followed after a varying period by ophthalmoplegia involving the oculomotor nerve to a varying degree. The headache may persist for only five days (case 5), or it may last for six weeks (case 3); in other instances it may be present intermittently for months, or there may be a background of what is usually regarded as migraine for many years (case 7). The onset may be with paralysis of the oculomotor nerve (case 6), but usually the oculomotor paralysis follows the headache, either immediately or after an interval of hours or days. In still other instances rupture of the aneurysm ushers in the disease (case 7). The headache is almost always unilateral, on the same side as the aneurysm, and is associated with pain in and above the eyeball on the affected side (cases 1, 2, 3, 4 and 5). In cases in which the pain begins in other parts of the head, it settles eventually in the eyeball (case 3), and at times it involves the entire side of the head (cases 2 and 7).

There is nothing in the headache which distinguishes aneurysm of the posterior communicating artery from aneurysm elsewhere in the brain. It is the oculomotor paralysis which indicates involvement of the vessel in question because of the intimate anatomic relation of the oculomotor nerve to the posterior communicating artery. Unfortunately, aneurysm involving the internal carotid artery may cause oculomotor paralysis, but in this case there is often involvement of the optic nerve or of other adjacent cranial nerves. If, in a suspected case of intracranial aneurysm, there is isolated paralysis of the oculomotor nerve or paralysis of the oculomotor nerve with associated paralysis of the trochlear nerve, the probabilities favor aneurysm of the posterior communicating artery.

The practical point at issue is that aneurysm of the posterior communicating artery is usually smaller than that of the internal carotid artery and is therefore more accessible to ligation. There were 3 deaths among the 7 cases reported, but in case 7 the patient entered the hospital in profound prostration due to rupture of the aneurysm. Aneurysms of the posterior communicating artery are small, are usually accessible to ligation and constitute, therefore, a favorable type of cerebral aneurysm. Ligation may be followed by recession of the paralysis of the oculomotor nerve or there may be no change whatever in the ophthalmoplegia. In either case the primary object of ligation, prevention of rupture of the aneurysm, will have been accomplished.

DIAGNOSIS

Aneurysm of the posterior communicating artery must be considered a good possibility in a subject with recurrent headache, followed by oculomotor paralysis of varying degree. Little can be expected from

roentgenologic studies, since erosion of the skull is not usual. Some help may be obtained from the presence of retinal arteriosclerosis and/or roentgenologic evidence of calcification of the internal carotid arteries. These signs will not establish the diagnosis, but they may confirm it. The spinal fluid is normal except in those rare instances in which syphilis is the cause of the aneurysm, and in the more frequent circumstances of rupture of the aneurysm, when bloody or xanthochromic spinal fluid is found. There is little in the systemic examination which is significant in the usual case. Hypertension helps little in the diagnosis, except to raise the possibility of an aneurysm associated with arteriosclerosis, but most aneurysms are not associated with changes in the blood pressure. Endocarditis may raise the issue of mycotic aneurysm, also a rare possibility. In the last analysis, the clinical history and the demonstration of ophthalmoplegia referable to the third nerve will be the most important factors in the diagnosis of an unruptured aneurysm of congenital origin. The diagnosis may be established with certainty by arteriographic examination, but in almost all cases this procedure is unnecessary for the establishment of the diagnosis.

CONCLUSION

A series of 7 cases of aneurysm of the posterior communicating artery alone is reported.

The clinical history of recurrent headache associated with the development of ophthalmoplegia involving the third nerve appears to be the most significant feature in the diagnosis. There is little else which has been found to be helpful, except for the arteriogram.

In 4 of 6 cases operation was successful. In the seventh case death occurred before operation could be accomplished.

111 North Forty-Ninth Street, Philadelphia.

PENETRATION OF AUREOMYCIN INTO THE EYE

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THE EFFECTIVE use of aureomycin in treatment of several external infections of the eye has been reported by Braley.[1] Because of the possibility that aureomycin may be of value also for intraocular infections, the current study was undertaken to determine the penetration of this new antibiotic into rabbit eyes following various methods of administration.

TECHNIC

Topical Application.—The technic as described by von Sallmann[2] was used in iontophoresis, the corneal bath and subconjunctival injection. A fresh solution of 0.5 per cent aureomycin borate was made daily, distilled water being used as the solvent. After production of local anesthesia with 6 drops of 0.1 per cent dibucaine hydrochloride (nupercaine hydrochloride®), the applicator tube was filled to the halfway mark (2.5 to 3.0 cc. of solution). At the end of the procedure the excess fluid was carefully removed, and about 0.25 cc. of aqueous was withdrawn at stated intervals with a 27 gage needle on a tuberculin syringe. The amount of aqueous removed varied occasionally, depending on the size of the anterior chamber. In the iontophoresis experiment 1.6 milliamperes was employed with the cathode on the eye and the anode on the head of the animal. Anode iontophoresis was first tried but was abandoned because it caused excessive damage to the eye. One drop of fluorescein sodium was applied to the corneas four, twenty-four and, if necessary, forty-eight hours after treatment.

In the experiment with subconjunctival injection, 0.5 per cent aureomycin borate was dissolved in sterile distilled water or in 0.5 per cent procaine hydrochloride. When higher concentrations of procaine were used, aureomycin borate did not readily go into solution. After production of local anesthesia with drops of 0.1 per cent dibucaine hydrochloride, 0.5 cc. of the procaine-aureomycin solution was injected subconjunctivally in the region of the superior rectus muscle and 0.25 cc. of aqueous was withdrawn at stated intervals. The concentration of aureomycin in the aqueous was measured by the serial dilution method, as described by Dornbush,[3] and the end point was read at four hours. Since Dornbush's test

This study was supported in part by the Knapp Memorial Foundation.

The aureomycin for these experiments was obtained from Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

From the Department of Opthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

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requires at least a 1 cc. sample, the method had to be modified by using correspondingly smaller amounts of all solutions.

Systemic Administration.—Aureomycin hydrochloride, dissolved in distilled water, was given intravenously, intramuscularly and orally. For the intravenous and intramuscular procedures, 20 mg. of aureomycin hydrochloride per kilogram of body weight, dissolved in 5 cc. of distilled water, was injected into the ear vein and thigh muscles, respectively.

For the oral method, 50 mg. per kilogram of aureomycin hydrochloride in distilled water was administered, in the use of a wooden gag and a rubber stomach tube, the aureomycin being washed down with water to prevent any of the solution from remaining in the tube.

The animals were killed at various intervals by intravenous injection of pentobarbital sodium (nembutal®). Heart blood was taken; the eyes were enucleated, and a cisternal puncture was made in an attempt to obtain spinal fluid. The aqueous was then withdrawn and the eyes were dissected. The wet cornea, sclera,

TABLE 1.—*Aureomycin Content of Aqueous, Expressed in Micrograms per Cubic Centimeter After Local Administration of 0.5 Per Cent Aureomycin Borate Solution by Three Methods*

	Corneal Bath for 5 Min.		Cathode Iontophoresis at 1.6 Milliamperes for 5 Min.			Subconjunctival Injection of 0.5 cc., 2,500 Micrograms	
Hours after local administration...	½	1	½	1	2	½	1
	—	—	0.05	>0.05	>0.05	0.1	<0.1
	—	—	0.1	>0.05	>0.05	0.1	<0.1
	—	—	<0.1	>0.05	0.1	0.1	0.1
	—	—	<0.1	>0.05	0.2	<0.1	>0.05
	—	—	<0.1	0.1	0.1	<0.1	>0.05
	—	—	<0.1	0.1	0.1	>0.05	>0.05
	—	—	...	0.1	0.1	...	>0.05
	—	—	...	0.1	0.1	...	....

iris and ciliary body, lens and vitreous were weighed, and ground with Berkshire sand and a phosphate buffer solution, the latter also being used to wash down the weighing bottle, mortar and pestle. The ground-up material with the washings was transferred to a centrifuge tube and diluted to approximately twenty times the weight of the given tissue. It was necessary to calculate the dilution factor for each specimen, because varying amounts of buffer were required for the washings. Purposely, the least possible amount of buffer was used so that the dilution factor might be kept as low as possible. The material was centrifuged at moderate speed for twenty minutes, and the supernatant fluid was assayed for aureomycin concentration, employing the test previously described. Between the various steps of the procedure the material was kept in the refrigerator. The heart blood was allowed to cool and clot at room temperature, and the centrifuged serum was used for the bioassay.

RESULTS

Local Application.—Table 1 presents the results of topical application. Since 0.05 microgram per cubic centimeter is the end point in the method of bioassay used, smaller quantities of aureomycin, if pres-

ent in the aqueous, were not detected by this test. Because of the small amounts of aqueous and the nature of the test, which required at least 0.25 cc. of solution for the 0.05 microgram per cubic centimeter concentration and another 0.25 cc. sample for subsequent higher concentrations, it was technically impossible to test for 0.05 micrograms per cubic centimeter or for higher concentrations with aqueous from the same eye. This explains the use of the < and > signs in the tables.

TABLE 2.—*Distribution of Aureomycin in Aqueous, Ocular Tissues, Serum and Spinal Fluid, Expressed in Micrograms per Cubic Centimeter of Fluid or per Gram of Solid Tissue, Following Oral Administration of 50 Mg. of Aureomycin Hydrochloride per Kilogram of Body Weight*

Hours after oral administration.....	1	2	3	4
Cornea.....	—	—	—	—
	—	—	—	—
	—	—	—	—
	—	—	—	—
Sclera.....	—	—	—	—
	—	—	—	—
	—	—	—	—
	—	—	—	—
Iris and ciliary body.....	—	—	—	—
	—	—	—	—
	—	—	—	—
	—	—	—	—
Lens.....	—	—	—	—
	..	—	..	—
Aqueous.....	—	—	—	—
	—	—	—	—
	—	—	—	—
	—	—	—	—
Vitreous.....	—	—	—	—
	..	—	..	..
Blood.....	2.0	2.0	0.5	0.5
	2.0	1.0	1.0	0.5
	..	..	0.5	..
	..	..	..	..
Spinal fluid.....	—	—	—	—
	..	—	—	—

The corneal bath, while nonirritating and not causing any staining defect, did not introduce measurable quantities of aureomycin into the eye. Iontophoresis, on the other hand, secured in the aqueous amounts of aureomycin varying from 0.05 to 0.2 microgram per cubic centimeter. Fluorescein staining of the cornea after iontophoresis indicated small lesions of the epithelium of all eyes at four hours, with disappearance of the staining defect within twenty-four hours in all but 2 eyes. At forty-eight hours all eyes were clear, showing no congestion or staining defects.

Subconjunctival injection produced about the same concentration of aureomycin in the aqueous as did iontophoresis, but there was more irritation. After twenty-four hours there was severe conjunctival congestion, with some chemosis and slight conjunctival discharge. Yellowish discoloration of the conjunctiva at the site of the injection, still pronounced at four hours, disappeared at the end of twenty-four hours. At forty-eight hours there was some conjunctival congestion, but no

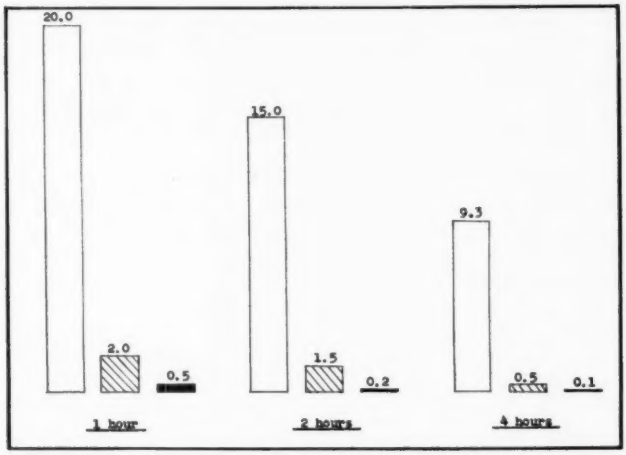
TABLE 3.—*Distribution of Aureomycin in Aqueous, Ocular Tissues, Serum and Spinal Fluid After Intramuscular Administration of 20 Mg. of Aureomycin Hydrochloride per Kilogram of Body Weight, Expressed in Micrograms per Cubic Centimeter of Fluid or per Gram of Solid Tissue*

Hours after intramuscular administration...	1	2	4
Cornea	—	—	—
	—	—	—
	—	—	—
	—	—	—
Sclera	—	—	—
	—	—	—
	—	—	—
	—	—	—
Iris and ciliary body	—	—	—
	—	—	—
	—	—	—
	—	—	—
Lens	..	..	—
	..	..	—
Aqueous	—	—	—
	—	—	—
	—	—	—
	—	—	—
Vitreous	—	—	—
	—	—	—
	—	—	—
	—	—	—
Blood	0.5	0.2	0.05
	0.4	0.2	0.1
	..	..	..
	..	..	..
Spinal fluid	—	—	—

chemosis or conjunctival discharge. These changes were noted in all the eyes treated, with only minor differences, and were most pronounced over the site of the subconjunctival injection.

Systemic Administration.—The oral and intramuscular methods, as shown in tables 2 and 3, showed no detectable amounts of aureomycin in the fluids and tissues of the eye or in the spinal fluid. The blood levels were rather consistent in relation to the amount administered and the time interval before the determination. The blood levels reached by the intramuscular route of administration were higher than those obtained by the oral method (chart).

The intravenous method of administration (table 4) produced fairly constant concentrations in the aqueous, varying from 0.05 to 0.4 micrograms per cubic centimeter, the concentration depending on the time of the test. The concentrations in the other tissues of the eye were more variable, ranging from 0 to 3.84 micrograms per gram of tissue, but at no time was aureomycin detected in the lens. The levels of the drug in the spinal fluid generally were slightly lower than the concentrations in the aqueous. The corcentrations in the blood were fairly uniform and were considerably higher with this method than with the oral and intramuscular methods.



Comparative blood levels of aureomycin, expressed in micrograms per cubic centimeter, following intravenous injection of 20 mg. of aureomycin hydrochloride per kilogram of body weight, intramuscular injection of 20 mg. of aureomycin hydrochloride per kilogram of body weight and oral administration of 50 mg. of aureomycin hydrochloride per kilogram of body weight.

Values for intravenous injections are represented by clear rectangles; values for intramuscular injection, by hatchures, and values for oral administration, by black areas.

COMMENT

Topical administration by various methods showed poor penetration of the drug into the anterior chamber of rabbit eyes. The 0.5 per cent solution was used because, according to Braley,[4] higher concentrations are irritating to the eye. The corneal bath gave no detectable amount of aureomycin in the aqueous. Iontophoresis and subconjunctival injection produced approximately the same aqueous levels; but, while the side effects of iontophoresis were temporary and negligible, subconjunctival injection produced considerable irritation and damage.

4. Braley, A. E.: Personal communication to the author.

Harned [5] found the drug highly irritating if given subcutaneously or intramuscularly. This irritating effect is somewhat overcome by combining aureomycin with procaine. When the aureomycin-procaine solution was tested against controls, its antibacterial activity was found to be the same as that of aureomycin in distilled water.

According to the principles of ionic transfer, anode rather than cathode iontophoresis should be used with aureomycin borate, since the aureomycin is present as a cation. However, anode iontophoresis

TABLE 4.—*Distribution of Aureomycin in Aqueous, Ocular Tissues, Serum and Spinal Fluid Expressed in Micrograms per Cubic Centimeter of Fluid or per Gram of Solid Tissue, After Intravenous Administration of 20 Mg. of Aureomycin Hydrochloride per Kilogram of Body Weight*

Hours after intravenous administration	½	1	2	4	6	8	12	18	24
Cornea	Trace	—	Trace	1.2	Trace	Trace	Trace	—	—
	—	—	1.5	1.4	Trace	—	—	—	—
	—	1.0	1.0	1.6	—	1.3	—	..	..
	—	1.0	1.6	1.6	—	1.3	—	..	..
	—	2.4	1.4	1.6	1.4	1.7	...	..	..
	—	2.6	1.5	2.9	1.8	1.2	...	..	..
Sclera	1.0	1.4	1.0	2.5	1.2	0.7	1.0	—	—
	1.2	2.0	0.6	1.7	1.2	1.5	1.3	—	—
	1.2	1.9	1.1	1.3	0.9	1.0	0.6	..	..
	1.6	2.2	1.3	1.4	0.9	1.0	1.0	..	..
	0.5	3.8	2.1	1.2	1.2	1.7	...	..	..
	0.9	2.3	2.3	2.1	1.2	1.3	...	..	..
Iris and ciliary body	—	1.9	—	1.6	1.5	—	—	—	—
	—	2.3	—	1.4	1.4	—	—	—	—
	3.1	0.9	1.4	1.5	Trace	—	—	..	..
	3.1	1.7	1.4	1.4	Trace	—	—	..	..
	1.4	2.2	1.7	1.5	1.4	—	...	..	..
	1.1	2.9	1.3	1.5	Trace	Trace	...	..	..
Lens	—	—	—	—	...	...	Trace	—	—
	...	...	—	...	...	...	—	—	..
Aqueous	0.1	0.1	0.2	0.4	0.2	0.1	0.1	0.05	—
	0.2	0.2	0.2	0.2	0.2	0.1	0.1	0.05	—
	0.2	0.2	0.2	0.2	0.1	0.1	0.05	—	—
	0.2	0.1	0.2	0.2	0.1	0.1	0.1	—	—
	0.4	0.2	0.2	0.2	0.1	0.2	...	..	..
	0.2	0.1	0.2	0.2	0.1	0.1	...	..	..
Vitreous	Trace	—	—	0.1	0.1	0.05	0.05	—	—
	—	—	—	0.05	...	0.05	0.05	—	—
	...	...	0.1	—	—	Trace	—	..	..
Blood	30.0	20.0	10.0	10.0	8.0	5.0	2.0	0.5	0.2
	20.0	20.0	20.0	8.0	5.0	5.0	1.0	0.5	0.2
	50.0	30.0	15.0	10.0	5.0	5.0	...	..	..
Spinal fluid	0.0	0.2	0.2	Trace	Trace	0.1	0.05	Trace	—
	...	...	0.1	0.05	0.05	0.1	Trace	—	..
	...	...	...	0.1	0.05	...	...	..	..

with aureomycin produced such a severe reaction, marked corneal haziness and large staining defect that it was not considered safe; therefore cathode iontophoresis was used, which was relatively well tolerated. This reversal of the poles probably limits the penetration of the drug into the anterior chamber, as von Sallmann [6] showed in the case of penicillin iontophoresis, but was necessitated by the difficulties mentioned.

5. Harned, B. K., and others: The Pharmacology of Duomycin, Ann. New York Acad. Sc. **51**:182 (Nov.) 1948.

6. von Sallmann, L.: Controversial Points in Ocular Penicillin Therapy, Tr. Am. Ophth. Soc. **45**:570, 1947.

The question arises as to the probable antibiotic effect of aureomycin in concentrations obtained in the aqueous by local application. In vitro sensitivity tests for aureomycin against common pathogens of the eye were performed by Dornbush.[7] His results collaborated the findings of the present study, in which twenty-two strains of hemolytic, coagulase-positive and mannitol-positive Staphylococcus aureus were examined. They showed inhibition by 0.1 to 1.0 microgram of aureomycin per cubic centimeter of solution, a concentration which was about the same as that obtained by topical administration. It is known that in the case of penicillin, streptomycin and bacitracin [8] aqueous levels are much higher than the in vitro sensitivity end points of most strains of pathogenic Staph. aureus. Thus, it would appear that in the case of penicillin, streptomycin and bacitracin a considerable margin of safety exists, as expressed by the difference between the aqueous concentration of the antibiotic and its in vitro sensitivity. This margin of safety was not found to exist with aureomycin.

With the oral method of administration, 50 mg. per kilogram of body weight was chosen as the dose because it corresponds approximately to the amount given to adult human subjects (Braley [4] gave about 3 Gm. per twenty-four hours to the average adult of 60 Kg.). This amount showed no apparent toxic effect—no emesis or diarrhea—but gave very low blood levels and no detectable amounts in the eye. The intramuscular administration seemed painful to the animal; although it provided higher blood concentrations, it, again, did not penetrate the blood-aqueous barrier in measurable amounts. Absorption from the muscles seemed slow and inadequate, as shown by the relatively congested, edematous muscles at the site of injection after the animal was killed and dissected. This can be compared to the poor absorption of the drug from the subconjunctival injection. Both the conjunctiva and the muscle were edematous, swollen and yellowish several hours after administration of the drug. The irritating effect of the drug can be further seen with the intravenous method of administration; as long as the solution passed directly from the needle into the vein, the animal remained relatively quiet; but if small amounts of the solution leaked into the subcutaneous tissues, the animal became highly excited.

With relatively high blood levels obtained by intravenous administration, measurable concentrations of the drug were detected in various tissues. However, in all the solid tissues of the eye, zero results actually represented only the end point of the bioassay (0.05 micrograms per cubic centimeter multipled by the dilution factor previously mentioned).

7. Dornbush, A. C.: Personal communication to the author.

8. Locke, J. C.: Experimental Studies with Antibiotics (Bacitracin, Streptomycin, Penicillin) and Antibiotic Mixtures, in Intraocular Infections with Penicillin-Resistant Staphylococci, Proc. A. Research Ophth., June, 1948, to be published.

The average value for this dilution factor was 20; therefore $20 \times 0.05 = 1.0$, which means that actually concentrations less than 1.0 microgram per cubic centimeter were not detected with this test. This factor varied somewhat, being sometimes as low as 10 and sometimes as high as 30, depending on the least amount of buffer necessary for washing down the ground-up material. Therefore in a few instances results less than 1.0 microgram per gram were obtained.

An interesting feature was the slow rate of disappearance of the drug from the various ocular tissues. Six to eight hours after intravenous injection the concentrations were only slightly less than one or two hours after the injection, and the disappearance curve was flat. This observation was contrary to the results for other antibiotics when administered intravenously.

To rule out the possibility that aqueous inhibits the antibacterial activity of aureomycin, a series of experiments was carried out on normal rabbit aqueous. Aureomycin borate was diluted with broth to contain 2.0 to 0.2 microgram per cubic centimeter in different concentrations; the aureomycin solution was mixed with normal aqueous and then assayed, the conditions thus simulating those present in vivo. No inhibitory action was found.

The results reported in the present series of experiments indicate limitations of the applicability of aureomycin because of its irritating property and its slow absorption by the tissues. Another disadvantage is the rapid inactivation of the drug when kept in solution. It must be remembered, however, that the development of this antibiotic is in an early stage and that these disadvantages may be remedied in the near future.

SUMMARY AND CONCLUSION

Experiments were carried out to ascertain the penetrability of aureomycin into the normal rabbit eye, with the following results:

1. After corneal bath no aureomycin was detected in the aqueous.

2. Iontophoresis and subconjunctival injection produced low levels in the aqueous. Iontophoresis was fairly well tolerated by the eye, but subconjunctival injection was irritating to such an extent that it was considered contraindicated.

3. Aureomycin did not penetrate into the eye when given orally or intramuscularly, although blood levels were obtained with both methods.

4. The cornea, sclera, iris and ciliary body, aqueous, vitreous and spinal fluid showed appreciable concentrations of aureomycin when large amounts were given intravenously.

As compared with other antibiotics, aureomycin is more irritating and penetrates less readily into the eye; but once it has crossed the blood-aqueous barrier, it remains longer in the ocular fluids and tissues.

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USE OF TANTALUM FOR OCULAR DRAINAGE

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THE PURPOSE of the present study was to review past efforts designed to lower the intraocular tension by various types of seton operations and to devise new technics using laboratory animals and suitable human subjects. While the implantation of foreign materials into the eye for the treatment of glaucoma has not been well accepted, either in principle or in ophthalmic practice, the literature contains several enthusiastic reports of this type of procedure.

HISTORICAL REVIEW

In 1906 Rollet and Moreau [1] reported 18 cases in which they treated hypopyon associated with corneal ulcer by a double paracentesis of the lower portion of the cornea, through which punctures a horsehair was threaded. Either end of this seton was glued to the cheek with collodion, and the thread was left in situ for forty-eight hours. The next year Rollet [2] applied this procedure to the treatment of 2 patients with painful absolute glaucoma with satisfactory results. He suggested that such a technic might be useful in the treatment of inflammatory glaucoma.

In 1912 two Englishmen, Zorab and Mayou,[3] working independently, in the same issue of the *Ophthalmoscope* reported on methods of draining the anterior chamber by a permanent silk thread implant, the thread acting as a wick that drained under the conjunctiva. Mayou used a 5 mm. length of single thread knotted at one end which he introduced just anterior to the root of the iris in the lower temporal quadrant. He reported on the results of this treatment in 4 cases of glaucoma and, a year later, in an additional 10 cases.[4] In 11 of the

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This study was supported in part by a grant from the Chalfont Fund. The tantalum was furnished by the Ethicon Suture Laboratories.

1. Rollet, M., and Moreau, M.: Rev. gen. d'ophth. **25**:481, 1906.
2. Rollet, M.: Rev. gen. d'ophth. **26**:289, 1907.
3. Zorab, A.: Ophthalmoscope **10**:259, 1912. Mayou, M. S.: ibid. **10**:254, 1912.
4. Zorab, A.: Ophthalmoscope **11**:211, 1913.

14 cases the tension was controlled successfully. Zorab described two procedures; the first consisted in passing a silk suture under the conjunctiva through the corneoscleral junction, across the anterior chamber and out through the limbus on the other side under the conjunctiva. This produced a double subconjunctival wick, but the difficulty of passing the suture made him abandon this procedure in favor of a second procedure, described as "aqueoplasty." Aqueoplasty consists in inserting a double silk loop through a small superior keratome incision 2 mm. behind the limbus and burying it under a conjunctival flap. He reported 23 cases of glaucoma in which he used these technics. In 18 cases the tension was controlled; in 4 cases the silk was not retained, and in 1 case the tension was not controlled.

Three years later (1915) Wood[5] described 3 cases of absolute glaucoma in which he used the Zorab aqueoplasty technic to control the tension and pain. He was so impressed with the success in these cases and in those reported in the literature that he devised his own technic, using a Graefe knife with a hole in the distal end of the blade. After the knife had been used to transfix the sclera at about 11 and 1 o'clock just behind the corneoscleral junction, the hole was threaded and the knife was withdrawn. The suture was cut, leaving a double strand across the anterior chamber. The free ends were threaded on needles, and then they were carried in a fanlike manner under the conjunctiva, where they were buried. He presented 2 cases in which this method was successful.

Vail[6] (1915) described a case of absolute glaucoma which he treated by drainage of the vitreous. He used a no. 10 plaited black silk ligature, which was carried on a heavy needle through all the coats of the eye in the region of the ora serrata and carried back and out through the same layers. Each end of the suture was buried under Tenon's capsule, the thread resting on the episclera as far back as the equator. Vail reasoned that Tenon's space was better equipped to handle drainage than the subconjunctival space.

The Vail operation is of interest because of the later report of Weekers[7] (1922), who described a new principle in the treatment of glaucoma. Weekers expressed the belief that from the standpoint of where the damage is done, all glaucoma is essentially hypertension of the posterior segment. He stated that permanent decompression of the posterior segment is essential, and he proposed and used a little hollow gold cuff, 2 mm. wide and 1.5 mm. in height, to rest in a scleral trephine hole 7 mm. back from the limbus, buried under the conjunctiva and Tenon's capsule. He expressed the opinion that the

5. Wood, C. A.: Ophth. Rec. **24**:179 and 235, 1915.
6. Vail, D. T.: Ophth. Rec. **24**:184, 1915.
7. Weekers, L.: Arch. d'ophth. **39**:279, 1922.

gold implant was essential to prevent the scleral wound from closing, since his microscopic studies showed that posterior sclerectomies became closed over. He mentioned that the operation was performed in several cases of absolute glaucoma with good results and that gold was well tolerated by the eye.

The tolerance of the eye for gold was substantiated by Stefansson [8] (1925), who reported its use in the form of a T-shaped insert in a keratome incision at 12 o'clock. The vertical portion of the T extended into the chamber, while the two limbs rested on the sclera, buried under the conjunctiva. In some cases a twisted gold wire was used; in others, a hollow tube, and in some, a solid gold implant with a spiral vertical portion. The chief complication seen was the puncture of the conjunctiva by the gold wire, in 2 of the early cases. The implant became dislocated in 1 case, and atrophy of the iris was observed in a few cases in which the gold came in contact with the iris. In the average case the follow-up period was three years, although in some the period of observation was only a few weeks. A total of 32 eyes were treated by this method, and the pressure was controlled in 80 per cent.

The first to use implants in the suprachoroidea was Row [9] (1934), who performed cyclodialysis and introduced a platinum-iridium wire experimentally into the cleft. The procedure was too traumatic and a cataract developed. Horsehair proved to be more satisfactory but had to be introduced with a grooved director as a guide. In 3 cases of glaucoma in man the condition was controlled with cyclodialysis and horsehair implants. Row emphasized the importance of burying the ends of the horsehair under Tenon's capsule to avoid having the stiff end work its way out through the conjunctiva.

A modification of the old Zorab operation was described as recently as 1936 by Wolfe and Blaess.[10] At 5 and 7 o'clock small conjunctival flaps were turned down, and two small keratome incisions were made into the chamber at the limbus. A lacrimal needle was employed to carry the thread across the chamber through the keratome incisions. The authors reported 6 cases in which this treatment was successful. They mentioned the value of subconjunctival manipulation of the suture in the event of a later rise of tension.

Troncoso [11] (1940) ingeniously proposed magnesium to be used as an implant after cyclodialysis. The magnesium was introduced into

8. Stefansson, J.: Am. J. Ophth. **8**:681, 1925.

9. Row, H.: Operation to Control Glaucoma: Preliminary Report, Arch. Ophth. **12**:325-329 (Sept.) 1934.

10. Wolfe, O. R., and Blaess, M. J.: Am. J. Ophth. **19**:400, 1936.

11. Uribe Troncoso, M.: Cyclodialysis with Insertion of a Metal Implant in the Treatment of Glaucoma: A Preliminary Report, Arch. Ophth. **23**:270 (Feb.) 1940.

the cleft and by the end of two weeks the metal had disappeared. The rapid oxidation was attended with a moderate inflammatory reaction and the production of hydrogen bubbles and ultimately by pockets of fibrosis in the cyclodialysis tunnel. A thin but dense fibrous capsule formed around gas bubbles trapped in the suprachoroidea. In no eye examined could a continuous channel be demonstrated. There were proliferative changes in the pigment epithelium, scattering of pigment and small round cell infiltration. Troncoso reported on 10 human eyes, 7 of which had had previous operations. There were good results in 2 eyes, apparently good results in 4 and poor results in 4.

EXPERIMENTAL STUDY

A review of the literature has shown that a subconjunctival implant at the limbus is poorly supported and easily displaced and that it tends to erode through the conjunctiva. This was confirmed in preliminary experiments in rabbits, and for this reason attention was directed to suprachoroidal drainage.

Cyclodialysis is one of the accepted methods in the treatment of glaucoma. It is effective only so long as the chamber angle remains open. When the cleft closes, the tension rises. If one could prevent the reattachment of the ciliary body after cyclodialysis, one should be able to maintain suprachoroidal drainage. To prevent this reattachment, a wedge of physiologically acceptable material placed in the cyclodialysis cleft should provide drainage. Tantalum, according to Burke,[12] is the most inert metal known, having a half-life of 955 years in concentrated sulfuric acid at 147 C. The lack of reactivity is due to the fact that a tenacious oxide film forms on its surface, preventing the transfer of electrons to the tissues. Studies of the tolerance of extraocular tissues to this substance indicate that a single layer of fibroblasts forms around a tantalum implant with no inflammatory response. A study of the ocular reactions to tantalum was therefore undertaken.

Reaction of the Eye to Tantalum.—The first study was concerned with the reaction of the eye to a piece of tantalum wire inserted into the anterior chamber. Under sterile precautions, a 4 mm. length of tantalum wire was inserted into the anterior chamber of albino rabbits by loading a 22 gage, 1½ inch (3.8 cm.) needle. The cornea was pierced with the needle, and the tantalum wire was pushed into the chamber by means of a stylet.

The reactions of 12 rabbit eyes were studied, and eyes were removed serially at one, three, five and eight days. Four eyes were observed

12. Burke, G. L.: Corrosion of Metals in Tissues: an Introduction to Tantalum, Canad. M. J. **43**:125-128, 1940.

for two and one-half months and 2 for six months. Except for slight infiltration at the site of paracentesis, the corneal reaction was nil. For a day or two after the paracentesis the vessels of the iris showed some dilatation, which subsided by the third day. In some eyes a small amount of fibrin formed around the implant where it adhered to the iris; this disappeared in a few days, and the tantalum fell into the chamber angle below.

The microscopic reaction to the tantalum was studied in two ways. It was felt desirable to study the reaction with the metal in situ. The eyes were fixed in dilute solution of formaldehyde U. S. P. (1:4) for twenty-four hours, and then the iris was dissected out and washed in distilled water, care being taken to prevent the tantalum from becoming dislodged. The anterior surface was then painted with hematoxylin by means of a camel's hair brush to stain the endothelial cells and the cells of the anterior stroma. The irides were then cleared in the routine manner and mounted in full thickness for study.

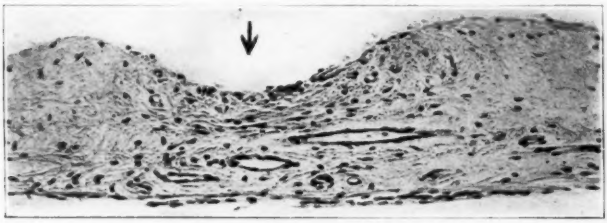

Fig. 1.—Tantalum wire had been in contact with the iris for a week (arrow). A few mononuclear cells are present, but no inflammation. The endothelial surface of the iris appears intact.

At the same time, routine meridionally cut sections were made after fixation in Zenker's solution. To prepare these sections it was necessary to remove the metal before sectioning, but the eyes were cut through the area from which the tantalum had been removed.

Microscopic study indicated that there was no inflammatory response at the site of contact between the uvea and the tantalum. A small amount of fibrin formed on the surface of the tantalum. This was attributed to the high fibrin content of the rabbit's secondary aqueous rather than to any reaction evoked by the tantalum. In no section was any inflammatory reaction observed (fig. 1).

The tissue acceptability of tantalum was also demonstrated by implanting 26 gage wire into the midstroma of the cornea. The implantation was accomplished by loading a 3 mm. length of wire into a 22 gage needle, which was inserted into the midstroma of the

cornea. The wire was ejected into the stroma by a stylet. Tantalum was compared with silver, a copper alloy and with stainless steel. The results are summarized in figure 2, which shows that tantalum remained longer than any of the other materials tested. There was no inflam-

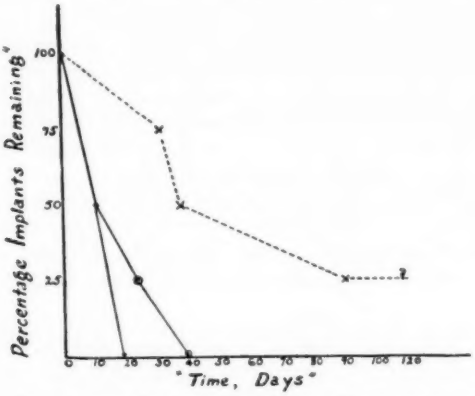

Fig. 2.—Tissue acceptability of various types of intralamellar corneal implants. Values for tantalum are shown by the broken line; values for silver and a copper alloy, by the line with solid dots, and values for stainless steel, by the line with hollow circles.

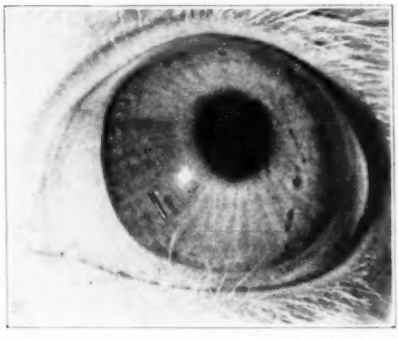

Fig. 3.—A small piece of tantalum wire implanted in the corneal stroma showed no reaction at the end of four weeks.

matory reaction in the cornea around the tantalum, whereas the other materials produced varying degrees of inflammation (fig. 3). One tantalum implant remained for four months, at which time the animal was used for another experiment.

Use of Tantalum Wire.—A series of preliminary operative procedures was undertaken in which braided tantalum wire loop was used in several ways. In 2 albino rabbits it was used as an inclusion in a keratome incision into the anterior chamber. The ends of the wire were buried under a conjunctival flap. In 2 other animals it was placed in contact with the anterior surface of the lens through a keratome incision made directly through the ciliary body. The ends were buried under the conjunctiva. In another 2 rabbits the tantalum wire was used as an implant in the suprachoroidea. It was observed that tantalum was well tolerated at these sites, that the operative wounds healed well and that the eyes remained quiet for four months without inflammatory or degenerative changes. It was noted that the tantalum wire cut through the conjunctiva when it was buried near the limbus. The tantalum wire in all operative sites was incorporated in the scar and seemed to form an integral part of the wound. Fibroblasts grew into the meshwork of the braided tantalum. India ink was injected into the anterior chamber of these eyes. In 2 animals with the keratome incisions near the limbus a small amount of ink could be observed under the conjunctiva near the wound. In the other animals the ink was difficult to trace and none appeared to pass through the scleral wounds, although it followed the path of the tantalum wire as far as the sclera. It was concluded that tantalum wire could be of no assistance in the development of a fistula, since the fibroblasts grew into the interstices of the wire, incorporating it into the tissues.

Use of Tantalum Plates.—Special cyclodialysis implants were prepared by Mr. A. Goebbels, of the Wilmer Ophthalmological Institute. These implants were 2 mm. wide and 9 mm. long and were bent on a radius of curvature of 7 mm., which corresponds closely to that of the curvature of the rabbit's sclera. The edges were carefully rounded, and the implants were polished with jeweler's rouge. The posterior 2 mm. of the implant was bent at about a 120 degree angle with the main portion of the implant. This provided a small lip, which was held firmly by a mosquito clamp in inserting the plate into the cyclodialysis cleft. This lip projected out through the sclerectomy wound and could be seen through the conjunctiva after the flap had been sutured. In the rabbit it was necessary to start the cyclodialysis well back, almost at the equator, about 8 mm. from the limbus, to prevent getting into the ciliary sinus instead of the suprachoroidea. It was found necessary to use a sharpened cyclodialysis spatula to cut through the firm attachment of the ciliary body to the sclera. With this sharpened instrument, care was exerted not to injure Descemet's membrane. At the termination of the procedure, the end of the implant

could be seen in the angle by placing a little pressure on the sclera above the implant. Hemorrhage was avoided by keeping away from the long ciliary vessels.

Eight operations with tantalum implantations were performed. Four cyclodialyses without tantalum implantations were done as controls. In 4 of the 8 eyes, the implants were removed at the end of four weeks. It was noted at the time of removal that there was a free flow of aqueous on the incision of the conjunctiva overlying the posterior

Fig. 4.—The suprachoroidal endothelium-lined cleft between the iris and ciliary body, below, and the corneoscleral junction and sclera, above, provided a free channel of drainage from the anterior chamber to the episcleral tissues. The tantalum had been in place two months and had been removed just prior to fixation.

lip of the implant. There was no apparent scarring of the subconjunctival or episcleral tissues, and the implants slipped out with ease. A month later gonioscopy revealed the cleft to be wide open in 1 eye, to be partially closed over in 2 eyes and to be completely closed in the fourth eye. The cyclodialysis clefts of the 4 control eyes were completely closed by the second week. In the other 4 eyes, the

tantalum implants were permitted to remain for a total of eight weeks. In these eyes, 0.1 cc. of a 2 per cent solution of fluorescein sodium in a tuberculin syringe was mixed with the aqueous through an oblique puncture wound in the cornea. No pressure was exerted, and the syringe, containing 0.1 cc. of the aqueous-fluorescein mixture, was withdrawn. In a few moments one could observe the fluorescein subconjunctivally about the sclerotomy end of the tantalum implant. On incision of the overlying conjunctiva, a free flow of greenish fluid was observed. These eyes were removed for histologic examination. A

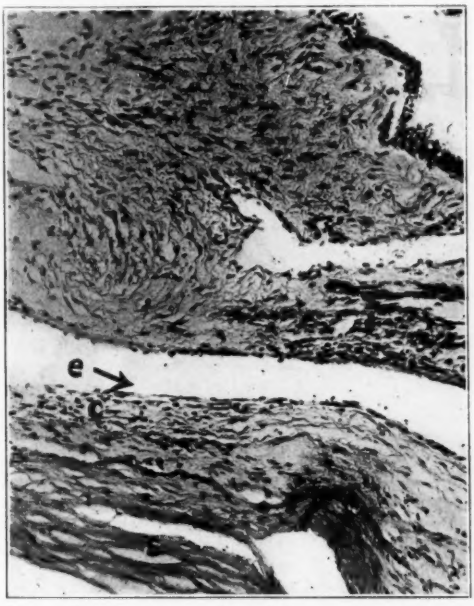

Fig. 5.—The midportion of the channel between the ciliary body and the sclera shows a loose network of connective tissue (*c*) between the endothelial lining (*e*) and the sclera (*s*).

small pannus was observed in 3 of the 8 rabbit eyes in the region of the implant.

It was concluded that tantalum acted as a physiologically acceptable wedge between the ciliary body and the sclera and that the aqueous could filter around the implant and out the sclerotomy wound to the episcleral tissues.

Pathologic Studies.—Microscopic examination of the 4 eyes that carried implants for two months showed plainly that a continuous cleft

ran from the chamber to the episclera (figs. 4, 5 and 6). The tantalum became lined with a layer of flat cells, which were indistinguishable from the endothelial cells on the anterior surface of the iris. On the scleral, as well as on the ciliary, side of the cleft, underlying this endothelial lining was an area of loosely organized connective tissue. From the anterior edge of the sclerotomy wound a rather dense mass of episcleral connective tissue appeared to be growing downward and forward into the suprachoroidea. This connective tissue, as well as the posterior lip of the sclerotomy wound, was covered with the same layer of endothelial cells as that which lined the rest of the cleft.

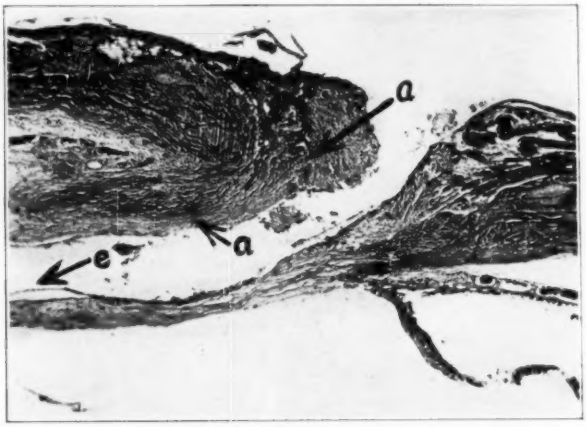

Fig. 6.—At the posterior end of the channel from the anterior chamber to the episcleral region, a downgrowth of episcleral fibrous tissue (*a*) turning forward into the cyclodialysis tunnel is observed. The tantalum plate was removed prior to fixation. The endothelial lining (*e*) is well seen.

TANTALUM IMPLANTS IN HUMAN SUBJECTS

On the basis of the microscopic observations, which showed absence of inflammatory reaction and a thin layer of endothelial cells lining the cyclodialysis cleft, it was considered justifiable in certain desperate cases to undertake the treatment of glaucoma with tantalum implants. In view of the downgrowth of episcleral fibrous tissue into the cyclodialysis tunnel in the rabbit, it was considered wise to modify the procedure of tantalum implantation for the human eye.

In order to avoid episcleral tissue downgrowth, it was decided to bury the tantalum plate in the suprachoroidea. For this purpose, implants 2 mm. wide, 0.25 mm. thick and 8 mm. long, bent on a radius

of curvature of 11 mm., were prepared. They were highly polished, with rounded edges. One millimeter from one end a 0.25 mm. hole was drilled, and a 00000 braided mylon suture was passed through this hole. The suture was secured by means of a square knot. One end of the suture was threaded on a small needle with a curved cutting edge. After cyclodialysis had been performed in the routine manner, the tantalum plate was inserted into the cleft by means of a curved smooth forceps. The braided nylon suture on the needle was employed to anchor the plate in the suprachoroidea. This was accomplished by passing the needle backward toward the equator of the eye in the suprachoroidal space for 2 mm. and out through the sclera, where it was tied to the other end of the suture. The suture was adjusted in such a manner that the exact position of the implant could be controlled. In each case the implant was placed so that the anterior end was visible at the limbus.

Five such operations were performed on 4 eyes. The first two operations were for congenital glaucoma; the third was for secondary glaucoma, and the last 2 operations were performed on a narrow angle type of absolute glaucoma.

REPORT OF CASES

Case 1.—C. W., a 1 month old boy with congenital glaucoma, had corneas which were enlarged and extremely hazy. Tension measured 30 mm. of mercury (Schiøtz) in each eye. A goniotomy was performed on the left eye. The intraocular pressure one week later was unchanged; so a cyclodialysis with tantalum implantation was performed. A week later the tension was 35 mm., and the implant was removed.

Case 2.—J. E. C., a 6 month old girl, had congenital glaucoma, with an intraocular tension of 35 mm. (Schiøtz) in the right eye and 55 mm. in the left eye. A cyclodialysis with tantalum implantation was performed on the left eye. One week later, the tension measured 5 mm., the cleft as seen gonioscopically was open and the cornea had cleared. The patient was sent home, and the tension remained controlled for three weeks, when it again became elevated. The implant was removed.

Case 3.—T. S., a 12 year old Negro girl, had had secondary glaucoma of the left eye for five months. She had had a congenital cataract, which was treated by discission and lavage at the age of 1 year. Three years later a discission of thickened capsule was performed. Five months before her present admission two cyclodialyses had been performed on the left eye. After the second procedure tension was controlled for five months. On her admission the eye was stony hard and vision was reduced to counting fingers. A cyclodialysis with tantalum implantation was performed. The pressure rose during the third week, and the tantalum implant was removed.

Case 4.—D. E. G., a 70 year old woman, was admitted with bilateral acute congestive glaucoma of one week's duration. There was no light perception in either eye. Tension measured 90 mm. (Schiøtz) in the right eye and 68 mm. in the left eye. She was given a course of furfuryl trimethylammonium iodide

(furmethide®) and the tension fell in the left eye to 34 mm. (Schiøtz). The patient refused enucleation; so iridencleisis was performed on the right eye and a tantalum implantation was performed on the left eye (fig. 7). The tension remained controlled for twelve days in the left eye, and the implant was removed. The tension then rose to 60 mm. The implant was replaced, but the tension did not fall below 40 mm. (Schiøtz). Gonioscopy one week after operation revealed the tantalum plate in the angle with a small mass of fibrin about it. There was no cyclodialysis cleft except at the point of emergence of the tantalum plate. The patient was followed for a year and one-half. A small pannus developed in the cornea adjacent to the implant. At the time of this report, the chamber was still fairly shallow, and the patient complained of ciliary pain on rubbing her eye. The eye remained white, and the braided suture, which could be observed readily, had caused no irritation under the conjunctiva.

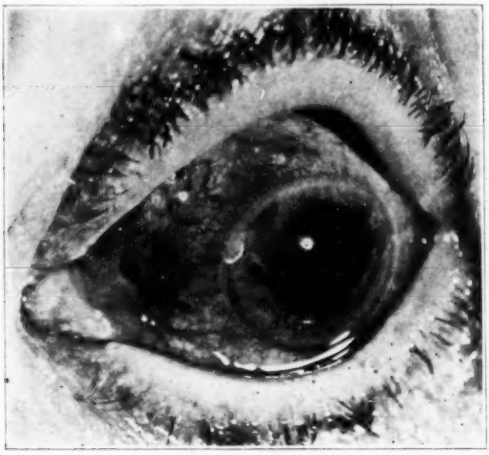

Fig. 7 (case 4).—Five days after the first operation, the tension was controlled. The implant was placed in the upper nasal quadrant.

Since in no case was the tension controlled for more than two weeks, it was concluded that mere separation of the ciliary body from the scleral spur did not constitute a functioning cyclodialysis opening. Failure in these cases was attributed to the prevention of effective suprachoroidal drainage by organization of an endothelium-lined tract about the implant. In the rabbit it had been noted that fluorescein drained about the implant when the implant came out through the sclerotomy wound. It was felt that failure in use of the implant in the human eye may have been due to the closure of the sclerotomy wound. The sclerotomy wound was closed in all instances when the second operation was performed for the removal of the implant. The use of an external fistulizing device seemed essential; for this reason, the investigation of various types of tubes was undertaken.

USE OF INTRAOCULAR TUBES

Stefansson was the first to report the use of intraocular tubes. His tubes were fashioned of gold, in the shape of a T and were implanted in a keratome incision in the superior part of the limbus. He found that the tension was controlled by using this device but that dislocation might occur. In order to get effective support from the tissues, and to avoid the limbal area, it was decided to use a tube running from the chamber angle through the suprachoroidal space to the episcleral tissues.

The first tubes to be employed were 24 gage platinum-iridium cannulas, made by cutting dental needles into 10 mm. lengths and bending them on a radius of curvature of 7 mm. The ends were smoothed and polished. Two such tubes were implanted in rabbits in cyclodialysis tunnels. The episcleral end projected backward

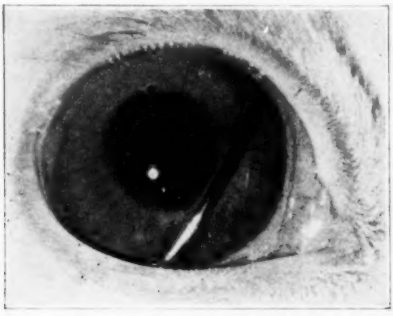

Fig. 8.—A platinum-iridium tube placed in the suprachoroidea had slipped into the anterior chamber. The photograph shows no reaction after the tube had lain in the chamber six months.

about 2 mm. beyond the sclerotomy wound, which was covered over with conjunctiva. At the end of the procedure the tube seemed firmly supported by the tissues, but after two weeks the tubes slipped into the chamber, where they remained for six months without causing any undue reaction (fig. 8). There was slight atrophy of the iris where the iris rubbed against the ends of the tubes. It was concluded that tubes had to be fixed in some way to prevent their shifting position.

When tantalum tubing became available, Mr. A. Goebbels, of the Wilmer Institute, prepared flattened tantalum cannulas for intraocular implantation in rabbits. These tubes were 9 mm. long, 2.5 mm. wide and 0.9 mm. thick, with an oval cannula 0.5 by 2.1 mm. They were bent on a radius of curvature of 7 mm. All edges were rounded and highly polished. The last 2 mm. of the convex side of the tube was removed, so that a hole 0.25 mm. in diameter could be drilled through

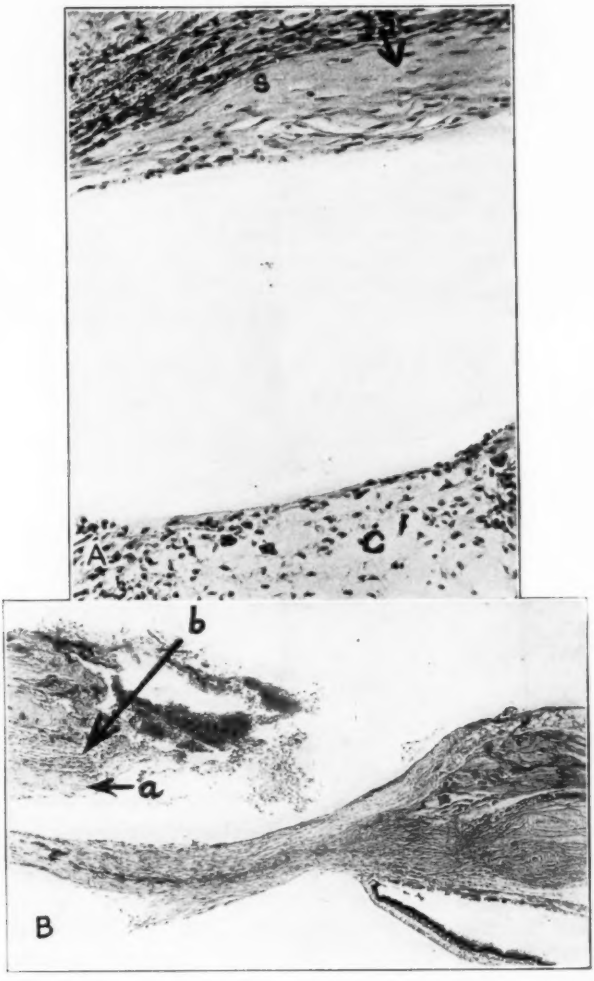

Fig. 9.—*A*, channel between the sclera (*s*) and the ciliary body (*c*) following removal of a tantalum tube.

B, posterior portion of a cleft following removal of a tantalum tube that had been in place nine months. This cleft is lined with endothelium. (*a*) A slight amount of fibrosis underlies the sclera; (*b*) there is no appreciable fibroblastic downgrowth from the episclera into the cyclodialysis tunnel.

the concave surface only. This edge was designed to rest on the sclera, where it was sutured with 00000 braided nylon.

Four such tubes were implanted in rabbit eyes in cyclodialysis tunnels and sutured to the sclera 2 mm. behind the sclerotomy wound. The anterior ends of the flattened tubes were permitted to project just beyond the limbus in 2 of the eyes so that they could be observed. The rabbits were followed for six months. In all 4 eyes a permanent corneal opacity developed at the limbus in the region of the implant. The further the tube projected, the larger was the opacity. A slight amount of episcleral injection persisted over the implant, but other than that the eyes showed no undue reaction and the media remained clear. Two animals were lost at the end of six months.

Nine months after implantation the remaining 2 eyes were studied as follows: A traction suture was taken in the sclera near the limbus and the eye rotated down so that the episcleral end of the tube could

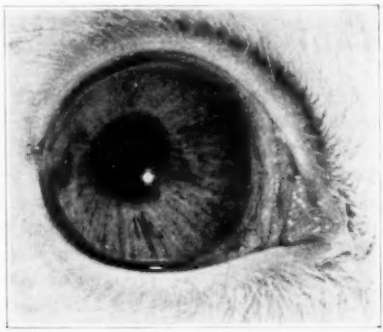

Fig. 10.—The eye one month after implantation of a tantalum tube shows a slight reaction and the presence of a permanent corneal opacity in the region overlying the anterior end of the tube.

be observed through the intact conjunctiva. One-tenth cubic centimeter of a 1 per cent solution of trypan blue in a tuberculin syringe was mixed with the rabbit aqueous through a 25 gage needle, which had been plunged obliquely through the limbus. The syringe was withdrawn with 0.1 cc. of a mixture of aqueous and trypan blue.

It was observed in both rabbit eyes that the trypan blue discolored the episceral tissues about the posterior end of the tube in a few minutes. The eyes were enucleated, the corneas were removed and a 27 gage hypodermic needle was inserted into the end of the tube. Trypan blue was injected, and there was further discoloration in the area about the implant. The nylon sutures holding the tubes in place were cut, but episcleral scar tissue had grown through the hole about the braided nylon suture and had to be divided to remove the implant. The episcleral end of the cannulas were free from tissue, and no

tissue had grown down into the tubes. The tubes slipped out with ease. The histologic picture was essentially the same as that observed with tantalum plates (fig. 9 *A* and *B*). There had been some downgrowth of episcleral tissue into the cyclodialysis tunnel, but this was not extensive.

It was concluded that, while there was no undue reaction, the development of corneal opacities and pannus in the region of the tubes was undesirable (fig. 10).

Even though tantalum is well tolerated by the tissues, the presence of some episcleral injection indicates that irritation is present. Since tantalum is inert, it is logical to conclude that the reaction must be due to the presence of a large, unyielding foreign body and that the irritation is of mechanical origin. The complaint of ciliary pain in 1 patient with a tantalum implant substantiated this observation.

SUMMARY AND CONCLUSIONS

The reactions of the ocular tissues to tantalum were studied. It was found that tantalum was well tolerated by the cornea, iris, ciliary body and sclera.

Endothelium-lined fistulas formed around tantalum plates inserted into cyclodialysis clefts. The channel ran from the chamber angle through the suprachoroidea and out onto the sclera. Episcleral fibrous tissue grew forward into the cyclodialysis tunnel for a short distance but did not interfere with drainage.

Four human eyes with glaucoma were treated with tantalum plates inserted into cyclodialysis tunnels. The tension was controlled for only two weeks. At the time of this report a tantalum plate has remained in an eye with absolute glaucoma for a year and a half. The tension remains at about 40 mm. of mercury (Schiøtz). The patient complains of ciliary tenderness under the implant. A small pannus has formed in the vicinity of the implant, but the eye has remained white and the media clear.

Experimental work on rabbits indicates that drainage of aqueous in the normal eye can be maintained by implanting a tantalum tube in the suprachoroidal space to extend from the chamber angle to the episcleral tissues. Local formation of pannus and injection of the episcleral vessels in these animals probably result from mechanical irritation by a rigid foreign body, which, though chemically inert, is too unyielding.

Further experimentation with similar devices should be more rewarding if a more flexible material capable of maintaining a lumen were used. Nylon tubing should be available shortly for study.

The use of a tantalum tube is justifiable as a temporary measure in desperate cases of glaucoma.

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CORNEAL TRANSPLANTATION IN CASES OF APHAKIA AND ECTOPIA OF THE LENS

Selection of Cases; Technic of Operations Outlined; Report of New Instruments

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CLEVELAND

THE PURPOSE of this article is to discuss the problem of corneal transplantation in cases of aphakia and displacement of the lens and to present a new technic and instruments for carrying out this type of operation in such cases.

Corneal transplantation has long been recognized as a highly successful procedure in properly selected cases; but there have been definite contraindications to this operation, and until recently the condition of aphakia has been considered unfavorable for operation (Rycroft and Somerset,[1] McArevey,[2] Filatov,[3] Elschnig,[4] Castroviejo[5]).

APHAKIA

It is now known that corneal grafts heal and remain transparent in aphakic eyes. Cases of aphakia are by no means the most favorable, but, owing to improved technics, a reasonably good chance of a successful corneal transplantation is offered in these cases.

In cases in which both corneal leukoma and cataract are present and it has been determined beforehand that the cataract exists, it is a much simpler and safer procedure to carry out the corneal transplantation first and the cataract extraction later, after a clear central area of cornea has been obtained. The operations when done in this order are the most satisfactory, and then only does the corneal transplantation procedure present no immediate problems. I have performed a number of such operations without the occurrence of unusual complications. These results agree with the experience of Castroviejo,[6]

From the Department of Surgery, Division of Ophthalmology, Western Reserve University School of Medicine and the University Hospitals of Cleveland.

1. Rycroft, B. W., and Somerset, E. J.: Corneal Graft in an Aphakic Eye, Lancet **2**:743, 1937.
2. McArevey, J. B.: Corneal Transplantation in an Aphakic Eye, Irish J. M. Sc. **142**:635, 1937.
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Elschnig and Filatov. However, in such cases, after the corneal transplantation has been successfully performed, there should be a considerable delay before removal of the cataract. At least six months should separate the two procedures to insure that complete healing has taken place. A cornea that reveals the diffuse scarring of interstitial keratitis, even though it has been quiescent for many years, may show reactivation of the keratitis after the extensive surgical intervention that is required when removing an area for transplantation.

This reactivation may reveal a typical picture of interstitial keratitis and be followed by complete opacification and a varying degree of vascular infiltration. Figure 1 shows such a case. The patient, a

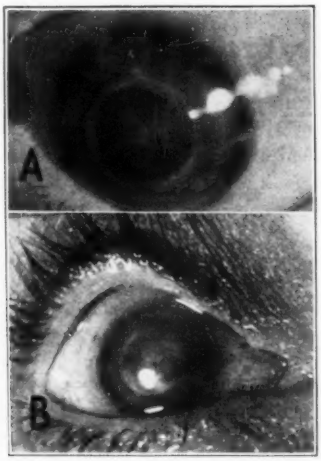

Fig. 1.—*A*, postoperative clear corneal graft; *B*, eye shown in *A* after active keratitis, resulting in opacity of graft.

woman aged 48, had old interstitial keratitis due to congenital syphilis. This had apparently been quiescent for many years. A corneal transplantation was done, and a clear graft was obtained (fig. 1 *A*). Three months after the operation, and before the cataract operation could be carried out, very active interstitial keratitis developed in this eye, which was followed by opacification of the graft with vascular infiltration and secondary glaucoma (fig. 1 *B*). This keratitis was presumably due to the trauma of the corneal transplantation, as the other eye remained quiescent throughout.

However, when the surgical procedures are carried out in the reverse order, or the cataract is removed first, the operation will progress without complications until the anterior chamber has been opened, and

then there may be an overwhelming loss of vitreous. This fact has been recognized for many years and has been reported in writing by Rycroft and Somerset, McArevey, Filatov and Elschnig. If the lens has previously been removed, there must be something in its place to keep the posterior segment intact, or as nearly intact as possible. This was early recognized by Filatov, who devised a spatula for insertion into the anterior chamber to hold back the vitreous. Theoretically, the condensation of the anterior surface of the vitreous body, commonly known as the hyaloid membrane, may keep the vitreous body intact, but the manipulation necessary in cutting the graft makes the presentation of vitreous into the anterior chamber very likely. If the cataract operation has been carried out by the extracapsular method, and the posterior capsule is intact, this membrane, of course, will act as a suitable barrier to the vitreous. When the cataract has been removed by the intracapsular method, the presence of vitreous in the anterior chamber, either as a herniation or as loose vitreous strands, is very common. Without adequate protection to the vitreous present in the anterior chamber, the maneuver of cutting the area of cornea to be excised will inevitably be followed by the escape of the vitreous through the central corneal wound. This loss of vitreous may be disastrous and be followed by complete collapse of the eye, especially if the vitreous is fluid.

Corneal transplantation in the aphakic eye can be performed successfully, but the operation presents special problems in regard both to the technic employed and to surgical judgment in selecting cases for operation. Many of these cases of opaque cornea in an aphakic eye present the end results of severe complications of cataract surgery, and the decision whether or not the eye should be subjected to further operation must be carefully weighed by the surgeon.

Types of Opaque Cornea in Aphakia.—The types of cases which can be considered in this category are: (1) cases of clear cornea that becomes opaque some time after the cataract operation has been done; (2) cases of corneal scarring due to keratitis following postoperative uveitis; (3) cases presenting both interstitial keratitis and mature cataract in which the cataract operation was done first and the resulting vision was not as good as had been anticipated.

1. In cases of the first type are both the corneal opacities that develop in aphakic eyes entirely independent of the condition of aphakia and the opacities that develop in transplantation, which are again unrelated to aphakia.

The many causes of corneal leukoma may occur in the aphakic eye, as well as in the nonaphakic eye, and the resulting impairment in vision must be remedied if at all possible; the same standards for choice of cases for corneal transplantation must be followed for both types of eyes.

Corneal transplants that remain clear for several months are reasonably certain to continue to be transparent; however, clear grafts have been seen to become opaque after a cataract operation has been done. It is known that, owing to systemic disease, trauma, infection or the onset of corneal dystrophy, clear grafts may become opaque at any time and that the opacification be unrelated to the previous operation. An example of this is a case of Groenouw's corneal dystrophy that progressed a number of years after an operation for congenital cataract (fig. 2 *A*). From its onset this condition had progressed, with the typical hyalin-like deposits in the superficial layers of the substantia propria. No vascularization took place, merely a gradually increasing haziness of the cornea developed. This condition indicated the removal

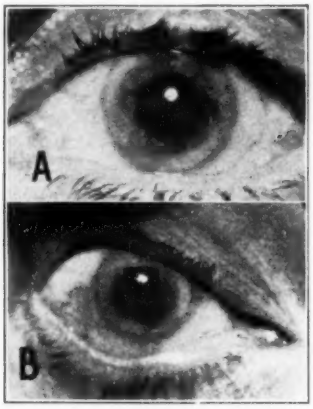

Fig. 2.—*A*, Groenouw's corneal dystrophy in an aphakic eye; *B*, Groenouw's dystrophy following corneal transplantation.

of the opaque cornea in the pupillary region and its substitution by a piece of clear cornea. However, since an intracapsular extraction had been done and examination with the slit lamp revealed the presence of vitreous in the anterior chamber, necessary steps had to be taken to prevent excessive loss of vitreous when the chamber was opened in performing the transplantation. Figure 2 *B* shows the postoperative appearance of this cornea.

I have had several cases of interstitial keratitis in which both corneal transplantation and removal of cataract were successfully performed, but in which at a later date there was reactivation of the interstitial keratitis with infiltration of blood vessels and opacification of the graft. This pathologic change is similar to that shown in figure 1. These

changes necessitate a second corneal transplantation. The choice of cases for the repeat operation requires special attention. One speaks of reoperating for corneal graft, but let it be remembered that the chance of success after corneal transplantation decreases in direct proportion to the number of times the operation is performed.

2. Various degrees of keratitis may follow postoperative uveitis. In most of my cases the condition followed extracapsular operations and the degree of uveitis varied a great deal. The cases in which the uveitis was severe and was associated with extensive vascular infiltration of the cornea fell into the unfavorable group for corneal trans-

Fig. 3.—*A*, dense vascularized scar following deep keratitis; *B*, deep keratitis with infiltration of large vessels.

plantation because of the nature of the infiltrate, and not because the eye was aphakic. In deciding in which of these cases the response to surgery will be good, the general indications and contraindications for corneal transplantation must be kept in mind and the criteria adhered to rigidly. It must be remembered that such cases represent at best the poorest operative risks; consequently, the greatest caution and care must be taken in selecting and preparing the patient when it is felt that benefit may be obtained by operation. Eyes with dense, vascularized scars without an area of fairly clear cornea that can approximate the graft are not suitable for transplantation. Figure 3 *A* illustrates such a case. However, it should be kept in mind that the blood vessels

can be dealt with and obliterated, by means of peritomy, cauterization or beta irradiation. Sometimes all these methods fail to obliterate the blood vessels. Surgeons who have been faced with this complication are well aware of the stubbornness with which the blood vessels resist obliteration. In cases of large, deep, isolated vascular trunks (fig. 3 *B*), I have found it helpful to cut down on these vessels and, with high magnification and the use of two electrodes, positive and negative, to cauterize the vessel directly. Patience and persistence are necessary.

In the cases of less severe uveitis it is often found that the infiltration has progressed somewhat farther toward the center of the cornea than has the vascular infiltration, or relatively clear areas of cornea may remain. In these cases the corneal transplantation can be carried

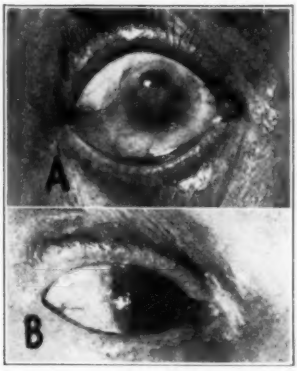

Fig. 4.—*A*, dense avascular corneal scarring following postoperative (cataract) iritis; *B*, eye shown in *A* after corneal transplantation, showing clear central corneal graft.

out after the necessary devascularization has been done. It is also important in these cases to allow a considerable period to elapse after the subsidence of the iritis before attempting the transplantation. Figure 4 *A* illustrates such a case, in which there was diffuse infiltration of the cornea with a relatively clear area in the upper half of the cornea near the limbus. Vascular infiltration of this cornea had not progressed more than 1 mm. beyond the limbus, and this only in scattered areas. Directly below the portion of cornea that is relatively clear was a hole in the posterior capsular membrane.

Corneal transplantation was done on this case, using the technic to be described. No vitreous was lost at the time of operation, and recovery was uneventful. Figure 4 *B* shows the postoperative clear central corneal graft.

In the foregoing types of cases it must be kept in mind that the existing pathologic condition predisposes to the occurrence of glaucoma and that even though this condition does not exist the so-called threshold, or margin of safety, may be narrow and further operative procedure may be enough to induce a condition of increased intraocular tension.

3. There is also the case that presents both a hazy cornea and mature cataract, and the surgeon has to decide whether or not the simpler operation of cataract extraction will be sufficient to restore the patient's

Fig. 5.—Clear corneal graft following transplantation in an aphakic eye.

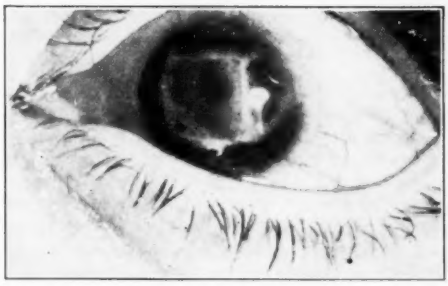

Fig. 6.—Postoperative opaque graft following transplantation in an eye with subluxation of the lens.

vision to a useful level. However, if the patient is not satisfied with the improvement after cataract operation, corneal transplantation must be considered. Such a case is illustrated in figure 5. In this case of trachoma of long standing the interstitial keratitis was not very dense, but vision was improved only to 20/100 after cataract operation. After corneal transplantation vision improved to 20/40, with correction. Figure 5 shows the eye after corneal transplantation.

DISPLACEMENT OF THE LENS

Surgeons readily know the likelihood of loss of vitreous in removing a subluxated or tremulous lens. The same problem is encountered in performing a corneal transplantation on an eye in which a subluxated lens exists, but the danger of loss of vitreous in these cases is enhanced by the extent of exposure of the anterior chamber and the length of time it remains open in cutting the graft. In most of these cases the diagnosis can be made before a corneal transplantation is done, but occasionally the corneal scarring is dense enough to obliterate the sig-

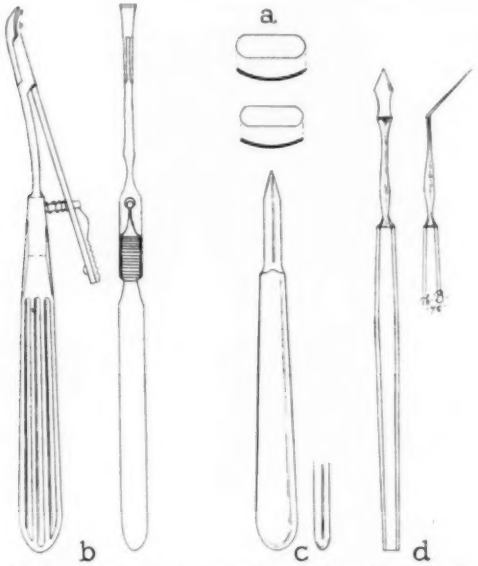

Fig. 7.—Special instruments for corneal transplantation in eyes with aphakia or ectopia of the lens: (*a*) curved corneal spatulas, (*b*) holder for spatulas, (*c*) magnet for stabilization and (*d*) special keratomes.

nificant clinical signs. When this occurs, the surgeon may not be aware that a dislocated lens exists until the anterior chamber is opened and vitreous presents in the wound. A hurried procedure to lessen the severity of this complication cannot then be carried out. The operation must proceed in the usual manner, but it can be made easier, and the possibilities of success are better, if this complication is prevented. Figure 6 shows a postoperative opaque graft in a case of subluxated lens. This condition was not known to exist until the anterior chamber was opened and the opaque portion to be replaced by graft was in the

process of being removed. Considerable vitreous was lost before the donor cornea was inserted. Of course, the cause of this opacity is open to speculation, and the failure of the graft to remain transparent may have been due to an inherent, incompatible tissue reaction; but in carrying out the precise surgical technic necessary in the corneal transplantation an attempt must be made to minimize every complication. The presence of unexplained opacity in corneal grafts is common enough without any unnecessary complication being added to the surgical procedure.

INSTRUMENTS

In order to improve the efficiency of the corneal transplantation operation on the eye in which either aphakia or dislocated lens exists, I devised the instrument presented here. Filatov described a spatula for use in this operation. However, his spatula requires a counterpuncture in the cornea, which is not desirable, and it does not possess a curve which approximates that of the cornea, a feature which insures more secure sealing off of the opening during the grafting.

Figure 7 illustrates the following instruments: (*a*) two spatulas or blades having an average corneal curve with rounded ends and measuring 6 and 7 mm., respectively, in diameter and 12 mm. in length; (*b*) a holder for the spatula, having a flat, grasping surface and an easy release mechanism; (*c*) a magnet for stabilization of blades, and (*d*) special and 7 mm. keratomes.

The other instruments necessary are the usual instruments for corneal transplantation, which include either the corneal trephine and curved scissors or the double-bladed knife and straight corneal scissors.

TECHNIC OF THE OPERATION

Anesthesia is obtained by an injection into the orbicularis muscle and a retrobulbar injection each of 2 cc. of 1 per cent procaine hydrochloride. Tetracaine and cocaine are instilled into the conjunctival sac at two minute intervals for ten doses of each drug. To insure complete dilation of the pupil and to reenforce the preoperative administered atropine, a subconjunctival injection of a preparation containing cocaine hydrochloride (4 minims [0.25 cc.]), 2 per cent homatropine hydrobromide (4 minims) and a 1:1,000 solution of epinephrine hydrochloride (12 minims [0.75 cc.]) is carried out in the perilimbal region of the four quadrants.

The area to receive the transplant is then marked with either the corneal trephine or the double-bladed knife, depending on whether a round or a square graft is to be inserted. This area is then stained with fluorescein sodium. The corneal sutures are inserted in the desired pattern and then drawn back away from the marked edge of the area to be removed. A central suture is inserted into the outlined area, making certain that this suture is deeply and well placed, as traction is necessary to remove the area satisfactorily. It is easier to cut the area out of its bed if the initial corneal markings have been carried rather deep into the cornea.

A small conjunctival flap is dissected free at the limbus on a line with the central area to be removed, and a corneoscleral suture is inserted at this limbal region. Either the 6 or the 7 mm. special keratome is then introduced and an incision the width of the keratome is made. On withdrawal of the keratome, the anterior

chamber is usually lost with the overflow of aqueous. The desired spatula or blade, corresponding in width to the keratome used, is then inserted into the special holder and this put through the limbal incision to the opposite side of the anterior chamber and placed firmly against this angle. The handle then releases the blade, and its free end can be steadied, if necessary, by the use of the handle magnet placed over the limbus. This may or may not be necessary, depending on the apparent stability of this spatula. Care must be exerted to keep close to the posterior surface of the cornea in inserting this blade so as to prevent

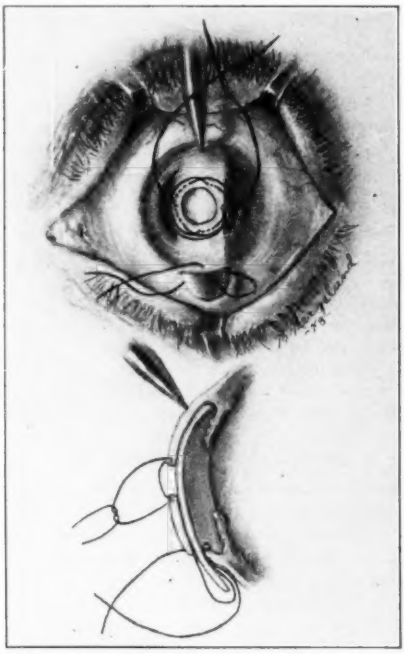

Fig. 8.—Drawing with spatula in the anterior chamber and the central area of cornea removed, ready to receive the graft. The cross section shows how securely the opening is blocked.

damage to whatever structures lie beneath. Its location must also be directly underneath the area of cornea to be removed.

The area of cornea to be removed is excised by first introducing a small cataract or discission knife along the marked border. After the incision is begun it is completed by the use of the special corneal scissors. When this central area is removed, it will be noted that the spatula is immediately underneath and blocking this opening, thereby preventing the overflow of vitreous, which otherwise would escape freely (fig. 8). The magnet applied to the limbus over the free end of the spatula holds this upward and firmly blocks the opening in the cornea

The donor cornea is cut in the usual way and replaces the area removed from the recipient cornea. The corneal sutures are then drawn over the graft, and the blade or spatula is withdrawn, using the special holder (fig. 9). The corneoscleral suture at the limbus is then drawn tight and the wound is closed. Atropine and an antiseptic ointment are instilled into the eye, and a dressing is applied. It is advisable to cover both eyes after this operation.

In some cases of aphakia and leukoma, the iris is often immobile and cannot be dilated very well. This condition was found to be present in the case illustrated in figure 3 *B*. Consequently, in order to help reform the anterior chamber and

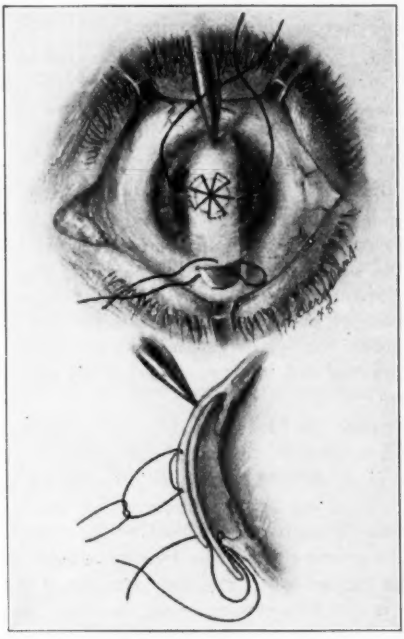

Fig. 9.—Drawing after graft has been inserted and the sutures have been tied. The spatula is now ready to be withdrawn.

prevent any anterior synechia, as the iris usually lies directly beneath the corneal wound, one may inject a small amount of isotonic solution of sodium chloride into the anterior chamber through the corneoscleral wound, previously closed.

The advantages of this instrument (spatula) are as follows:

1. The spatula is easy to manage. By means of the special holder, it can be introduced into the anterior chamber very much as one would insert a keratome. It can be kept in complete control until it has

reached the opposite angle of the chamber and is then easily released. Its stability and efficiency are enhanced by the magnet, which holds the free end upward against the cornea.

2. No counterpuncture is necessary for fixation. This necessitates a smaller corneal incision and lessens interference in metabolism and nutrition of the corneal graft.

3. The curve of the spatula more or less simulates that of the cornea, so that the spatula lies in close proximity to the inner surface of that structure. This, of course, tends to block any exit of intraocular fluid, which is the sole purpose of the feature.

4. The blades or spatulas that are introduced into the anterior chamber are of the exact same size as the keratomes used in making the incision. This provides for a tight fit around the end of the spatula and prevents unnecessary leakage of vitreous or of fluid from the anterior chamber.

Pitfalls of the operation are two:

1. Difficulty in cutting the recipient cornea. In removal of the area to be replaced by the graft, the initial puncture into the anterior chamber presents some difficulty, as the puncture must be made on a soft eye and, consequently, resistance is offered only by the traction upward by means of the central corneal suture and the very slight cutting resistance of the spatula in the anterior chamber. When the scissors can be introduced, the remainder of the cutting is relatively simple.

2. Prolapse of the iris. It is imperative to secure maximum dilation of the pupil before operation, for after the spatula is inserted the iris cannot be seen until after the operation is completed and the spatula is withdrawn. If the iris becomes incarcerated, its repair must wait until another time, when it can be freed by the method described by Castroviejo.[6] It apparently may be free immediately after operation but become incarcerated when the first dressing is done, forty-eight hours later. It is forcefully recommended, therefore, that the operation be preceded by instillation of sufficient atropine and a subconjunctival injection of a mydriatic at the time of operation.

COMMENT

The choice of cases of aphakia which are favorable for operation requires good judgment and a great deal of experience on the part of the surgeon. The case with a subluxated lens does not present this special problem.

The ideally favorable type of aphakia for operation is the interstitial keratitis of systemic origin that may become active after the cataract operation has been performed, but in which vascularization recedes

rapidly and completely, or the corneal leukoma of external origin that may follow ulceration or trauma.

The aphakic eye with little vascular infiltration may present no special problem or preoperative preparation. It is the aphakic eye with vascular infiltration and deep scarring that may require special attention and preoperative preparation. These eyes are often borderline candidates for glaucoma, a fact which should constantly be kept in mind. Then, again, further operative procedures may reactivate the underlying keratitis and the transplantation would probably be followed by failure, due to opacity of the graft.

Corneal grafts become opaque at times for inexplainable reasons, and it is necessary for the best results that the surgeon exercise all the means at his disposal to prevent this result through proper choice of cases and the minimizing of mechanical difficulties.

SUMMARY

Experience with corneal transplantation in cases of aphakia or displaced lens is summarized as follows:

(*a*) In cases of combined corneal leukoma and cataract the corneal transplantation should be done before the cataract is removed.

(*b*) Corneal transplantation can be performed on aphakic eyes that are properly selected and prepared, and when proper instrumentation is used for the operation.

(c) Ectopia of the lens also presents the problem of loss of vitreous, which must be prevented for the best results.

2. Instruments are shown and the technic is outlined for corneal transplantation in either the aphakic eye or the eye with ectopia of the lens.

3. The advantages of the instruments are outlined and the pitfalls of the operation stated.

Mr. Karl Kapp gave help in making these special instruments.

The instruments described are available through V. Mueller & Co., Chicago.

10515 Carnegie Avenue.

RELATION OF COLOR SENSITIVITY IN THE VISUAL FIELD TO THE LAMINAR PATTERN IN THE LATERAL GENICULATE BODY

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CHICAGO

A DETAILED study of the laminar organization in the lateral geniculate body of primates has been presented in an earlier paper.[1] In the present paper an attempt will be made to relate the distribution of color sensitivity in the visual field to the laminar pattern in the human geniculate nucleus.

The distribution of the transneuronal degeneration in the lateral geniculate body after localized retinal lesions, affecting portions of all three cell laminas related to each eye, has led to the inference [2] that the conducting unit in the optic nerve and tract from the retina is a three fiber unit. It has also been suggested [3] that the three fiber unit and the trilaminar pattern in the geniculate body may have a relation to the three fundamental colors of the Young-Helmholtz color theory. Some of the indirect evidence in favor of this thesis has been presented elsewhere.[4] It is of considerable interest at this point to utilize the recently obtained data on the human geniculate body in an attempt to correlate the regional variation in the laminar pattern with the distribution of color sensitivity in the visual field.

A close scrutiny of the distribution of the foci of secondary degeneration as depicted in the illustrations of Clark and Penman [2] reveals that a lesion in the peripheral retina was always followed by degeneration in one of the two sets of two cell laminas which constitute the projection zone of peripheral vision in the geniculate body. It may be argued, therefore, that if the conducting unit from the central area of the retina is a three fiber unit, that from the peripheral retina is a two fiber unit. If the postulation of a relation between a three fiber unit and trichromatic vision is permissible, it seems permissible also to consider a relation between a two fiber unit from the peripheral retina and dichromatic

From the Department of Anatomy, University of Chicago.

1. Chacko, L. W.: J. Neurol., Neurosurg. & Psychiat. **11**:211, 1948.
2. Clark, W. E. L., and Penman, G.: Proc. Roy. Soc. B. **114**:229, 1934.
3. Clark, W. E. L.: Tr. Ophth. Soc. United Kingdom **62**:229, 1942.
4. Clark.[3] Clark, W. E. L., and Chacko, L. W.: Nature **160**:123 (July) 1947.

vision. These suggestions, which have grown out of the experimental work on monkeys, appear equally applicable when one is considering the human lateral geniculate body, since the projection areas for peripheral vision in man are also composed of two sets of two cell laminas (each set being related to one eye). Other relevant anatomic observations on the retinal projection areas in the human geniculate body which now seem well established may be summarized as follows:

1. In the projection area for central vision of the human lateral geniculate body there are, in general, two sets of three laminas, each set belonging to one eye and consisting of one large cell layer and two small cell layers. The conducting unit, originating in the area for central vision of the retina of one eye and terminating in one geniculate mucleus, is a three fiber unit.

2. In a certain region of the area for central vision in monkeys, an extradifferentiation (splitting) of the fourth and fifth layers may be observed. An extradifferentiation is also seen in man, although it may assume a different pattern. These observations suggest, therefore, a tendency to evolve even a four fiber unit.

3. At the foveal center, the large cell elements being few or absent altogether, there are two sets of only two laminas, each set belonging to one eye and consisting of two small cell layers. The conducting unit in this case is a two fiber unit.

4. In the area for peripheral vision there are two sets of two laminas, each set belonging to one eye and consisting of one large cell layer and one small cell layer. The latter represents a composite layer formed by the fusion of the two small cell layers of the area for central vision. The conducting unit from each eye is, therefore, a two fiber unit, although of a type different from that in the center for foveal vision.

5. In the area for monocular vision the laminas and cells lose their distinctive features to a certain extent. This area may be considered the least differentiated part of the geniculate nucleus. The laminas are related only to the opposite eye, the uncrossed laminas being excluded from this region. The conducting unit originating in one eye is a two fiber unit.

6. The conducting fibers originating in the central portion of the retina and terminating in the large cell laminas appear to be relatively few, while those from the peripheral retina are predominant.

7. From an analysis of the experiments of Clark and Penman [2] it may be inferred that the smallest localized lesion in the retina results in transneuronal degeneration, the area of which is limited to a wedge-shaped region extending through the whole dorsoventral thickness of the lateral geniculate body. The number of laminas in the area thus affected depends on the position of the lesion in the retina. This means

that each locus on the retina is projected not on a point on the geniculate body, as the term "point to point" projection implies, but on a pyramidal slice of the nucleus. In the area of central vision in the nucleus, the apex of the pyramid is ventrally placed and directed toward the hilus, the large cell laminas being placed at this end of the pyramid. Layer 6 is located at the dorsally situated base of the pyramid. Such a portion of the geniculate body may be arbitrarily referred to as a "unit." Each such "unit" is then related to two corresponding points on the retinas of the two eyes. It always contains two sets of laminas, a "crossed" set, related to the point in the contralateral eye, and an "uncrossed" set, related to the point in the ipsilateral eye. The two sets contain the same number of laminas.

8. A characteristic mode of distribution of cells in the nucleus becomes manifest when the size of the cells in the various laminas is determined. Such a study [5] has revealed a regular cell size gradient in the laminas of the various projection areas of the geniculate body. For instance, the larger the size of the cells, the more numerous they are in the more ventrally placed laminas. The larger cells steadily decrease in number in the more dorsally placed laminas. The reverse is the case with the relatively smaller size cells in their distribution in the various layers. It follows from these data on the cell size gradient that the two sets of laminas (the "crossed" and the "uncrossed") comprising a single "unit" are not exact replicas of each other. The laminas of the two sets are so fitted together that they present the picture of a composite whole in each "unit," with transitions and continuous gradations. This means, for instance, that the size characteristics in one of the two sets of the three laminas related to one eye in the area for central vision are such that the complete picture of the continuous and finer gradient in the "unit" appears only if the gaps are filled in through the second set of laminas, related to the corresponding half of the other eye. Since the total number of laminas in any one "unit" in the various projection areas of the geniculate body represents the full quota of the constituent parts of the "unit" if the latter is to function with full efficiency in binocular vision, it is advisable to speak of an eight or a six fiber unit in the area for central vision, a possible four fiber unit in the foveal center, a four fiber unit of a different type in the area for peripheral vision and a two fiber unit in the area for monocular vision.

Turning from the anatomic data to a consideration of the regional variations in color sensitivity in the normal retina, I shall make special mention of some of the pertinent data available in the literature. Most observers obtaining data on the color sensitivity of the human retina have found that green and red are perceived only for a relatively

5. Chacko, L. W.: J. Anat., to be published.

short distance beyond the fovea and that the fields for blue and yellow extend farther out into the periphery. Ferree and Rand,[6] who used monochromatic lights of equal energy contents, concluded, however, that the visual fields for red, blue and yellow occupy the same area and that this area is less restricted than the field for green. Abney,[7] who also used spectral colors, found, under conditions of low or moderate illumination, that the fields for color vision increased in size in the following order: green, red, yellow and blue. A red-green mixture which matched yellow in hue and luminosity was found to have a considerably smaller field than pure yellow itself. Baird [8] tested the color sensitivity of the peripheral retina by recording the changes in color perception from the periphery of the retina toward the center. Red appeared yellow at the periphery and, passing through yellow-orange, was finally seen as red at the center. Green appeared yellowish at the periphery and gradually passed through greenish yellow to green. Yellow appeared as yellow throughout the transition but increased in saturation toward the center. A similar result was obtained with blue. Although it is not easy to equate the results of different observers, the consensus seems to be that, in contrast to the trichromasy of the central area of the retina, the periphery (at least under moderate degrees of illumination) shows dichromasy for blue and yellow. One may also mention the low sensitivity to blue at the center of the fovea, observed by Willmer [9] and others. Willmer assumed that the center is actually blue blind, owing to the absence of blue receptors. Thomson and Wright,[10] in their color-matching experiments, found an increase of sensitivity to blue light when the matching field was moved from the center toward the edges of the central fovea. Charpentier [11] published curves showing the sensitivity to colors in different parts of the field of vision. His curve for blue takes a sudden dip as it approaches the fixation point, indicating a lower degree of blue sensitivity in that region.

The question now arises: Has the regional variation in color sensitivity any relation to the structural characteristics of the geniculate body? Are there certain features of the laminar organization or of the cellular or synaptic morphology which contribute to a structural foundation for color perception? On the basis of the principle of a "point to point" projection an analysis of the relevant functional and anatomic data sug-

6. Ferree, C. E., and Rand G.: Am. J. Ophth. **3**:772, 1920.

7. Abney, W. de. W.: Colour Vision, London, 1895, Longmans, Green and Co.

8. Baird, J. W.: The Color Sensitivity of the Peripheral Retina, Washington. D. C., Carnegie Institution, 1905.

9. Willmer, E. N.: Retinal Structure and Colour Vision, London, Cambridge University Press, 1946.

10. Thomson, L. C., and Wright, W. D.: J. Physiol. **105**:310, 1947.

11. Charpentier, A.: La lumière et couleurs au point de vue physiologique, Compt. rend. Soc. de biol **8**:308, 1888.

gests the following correlations: The less distinct lamination of the narrow strip of the area for monocular vision is related to achromatic vision or to light sensations manifesting themselves as gray devoid of other specific chromatic attributes; the area for peripheral vision of the geniculate body, with its two sets of two laminas, is related to the color sensitivity of the peripheral retina, which confines itself chiefly to the blue and yellow regions of the spectrum; the area for central vision, with its greater differentiation into from six to eight laminas, is related to perception of colors comprising a larger range of the spectrum and a greater ability to recognize and discriminate various hues. The fact that at the foveal center the large cell layers of the geniculate body appear to contribute only a very small portion of the area for central vision, and, indeed, may be completely absent, lends itself to the interpretation that the large cell layers are related to blue perception. This interpretation seems to gain further support from clinical cases of toxic amblyopia reported by Rönne.[12] In these cases the degeneration of the papillomacular bundle, resulting in a central scotoma, was associated with a localized area of transneuronal degeneration in the lateral geniculate body. Particularly apposite are Rönne's cases of diabetic amblyopia, in which the color defects were perimetrically charted. It is generally known that in the milder forms of toxic amblyopia the sensitivity to green and red diminishes and disappears first whereas the sensitivity to yellow and blue remains undisturbed; with severe forms, perception of yellow and blue also becomes affected (Samelsohn, Rönne, Abney, Traquair, Duke-Elder). Thus, in Rönne's first case of diabetes there was complete loss of green perception for the total field, in addition to a central scotoma for red. In the second, severe case, perception for both green and red was lost, while the field for blue was intact except for a very small central scotoma for white. In the geniculate bodies in these cases, the small cell layers of the area for central vision had undergone profound degeneration, whereas the large cell layers were intact throughout their extent. The coincidence of the sparing of blue perception and the maintenance of the integrity of large cell elements is striking.

As regards the relation of the neural elements of the retina and the laminar pattern of the geniculate body to color vision, little has as yet been definitely established. Polyak [13] drew attention to the varieties of bipolar cells found in the retina and argued that, since maximum brightness of scotopic vision, as well as the maximum absorption and bleaching of visual purple of the rods, is concerned with the short wave portion of the spectrum, it is legitimate at least to hypothesize that the bipolar varieties related to the rods mediate impulses elicited by light

12. Rönne, H.: Arch. f. Ophth. **77**:1, 1910; ibid. **85**:489, 1913.

13. Polyak, S. L.: The Retina, Chicago, University of Chicago Press, 1948.

of shorter wavelengths, e. g., mop bipolar cells, and that the bipolar forms related to the cones transmit impulses preponderantly initiated by light of long and medium wavelengths. According to Polyak, the brush and flat bipolar cells, related to varying proportions of rods and cones, may be concerned with impulses elicited by the portion of the spectrum between green and violet. He emphasized the relation of the brush and flat bipolar cells to green and of mop bipolar cells to blue and violet. Similarly, he stated the belief that the midget bipolar cells presumably mediate impulses elicited by the long wave portion of the spectrum, approximately from red to green, with a probable emphasis on red. In connection with these suggestions, it is to be noted that the mop variety of bipolar cells is absent from the foveal center and that the midget bipolar cells are cruder and fewer in the extra-areal periphery of the retina.

With regard to the third neuron of the retina, the ganglion cells, one may summarize Polyak's histologic observations by saying that the larger these cells are, the thicker are their dendrites, the broader their dendritic expansions and the greater their number toward the periphery of the retina. Despite the complexity of the synapses in the retina, the neurons of a rod-dominated path form convergent pathways in a central direction and are of relatively larger size; it appears legitimate therefore to assume that the large ganglion cells, on account of their location in the course of a rod-dominated path, mediate impulses elicited by light chiefly of shorter wavelengths. On the other hand, the midget ganglion cells, establishing monosynaptic connections with midget bipolar cells, and through the latter with cones, may be concerned mainly with light of longer wavelengths. Polyak also stated that the thickness of the axons of the ganglion cells is commensurate with the size of the cell body, the larger ganglion cells having thicker axons. The large cells of laminas 1 and 2 of the lateral geniculate body are also found to have thicker axons and dendrites. Such facts and considerations seem to support a correlation between the large ganglion cells of the retina and the large size cells of laminas 1 and 2 of the lateral geniculate body. This tentative correlation is supported by the histologic details of Rönne's [12] cases of amblyopia, for he noted a selective degeneration of small (midget) ganglion cells in the fovea, whereas the large ganglion cells (which are also present in the fovea, but in the minority) were intact. As already noted, in these cases the degeneration in the geniculate body was confined to the small cell layers, the large cell layers being left unaffected. The importance of this observation of Rönne cannot be too strongly emphasized, in view of the fact that it is not practicable to bring about such selective atrophy by experimental methods in order to determine the specific connections between the third and the fourth neuron of the visual path. Thus, it

seems possible that the large ganglion cells in the retina are linked with the large cells in laminas 1 and 2 of the lateral geniculate body and that the latter are situated principally in the rod-dominated pathway of the visual system and therefore possibly mediate impulses elicited by light of shorter wavelengths. If it is assumed that in the projection zone for central vision of the geniculate body the large cell layers related to each eye subserve the blue region of the spectrum, the dorsally situated laminas, in which smaller cells are in the majority, may mediate impulses elicited by the longer wavelengths and the intermediate laminas may mediate impulses from the middle portion of the visible spectrum. The observed fusion of the third layer with the fifth and of the fourth layer with the sixth in the projection zone for peripheral vision might be considered as related to yellow, but not to red and green separately; in other words, it might be assumed that the impulses from the red and green receptors, even if the latter were present in the peripheral zone of the retina, would no longer remain segregated at the geniculate level or beyond it. If the thesis that the laminas of the geniculate body mediate impulses elicited by different portions of the visible spectrum is substantiated, the greater differentiation into extra laminas would imply the development of a mechanism to subserve finer gradations of hue.

Electrophysiologic investigations may throw light on this problem. Of special importance are Granit's [14] extensive studies on the spectral sensitivity of the retina. In a large series of experiments, he recorded potentials from one or a few fibers of the optic nerve. His results indicate that the receptors and neurons associated with a particular optic nerve fiber, while being sensitive to all parts of the visible spectrum, have a specific maximum sensitivity. Furthermore, it appears probable that further specificities are introduced by virtue of the fact that the optic nerve fibers from the different portions of the retina vary in caliber [15] from 0.7 to 10 microns. The differences in records of potentials as picked up from various optic nerve fibers depend on the wavelength of the stimulating light, on the sensitivity of the particular retinal elements stimulated and on the particular optic nerve fiber contacted for picking up the potentials. Thus, Granit's observations have led to knowledge of the spectral sensitivity of retinal elements connected with different optic nerve fibers. The optic fibers conducting impulses from retinal elements with specific sensitivity are sorted out when approaching the geniculate body and terminate in certain specific fields in it. These fields are the laminas, which, as has previously been indicated, are characterized by certain morphologic characteristics. The sum total

14. Granit, R.: Sensory Mechanisms of the Retina, London, Oxford University Press, 1947.

15. Chacko, L. W.: Brit. J. Ophth. **32**:457, 1948.

of activity of a particular lamina, then, will depend not only on its own special characteristics, but also on the number, quality and retinal connections of the optic nerve fibers terminating in it. In the light of these considerations, it appears likely, therefore, that the total activity of a particular lamina is concerned only with such events as are initiated by stimulation with light of a limited spectral range.

Although the observations reported here have been assembled in support of the thesis that the laminar pattern in the lateral geniculate body of the primates has a specific relation to color vision, evidence is only indirect and presumptive. Further evidence must be sought in four directions: (1) a study of localized electrical responses in the geniculate body following stimulation of the retina by light of different wavelengths; (2) a systematic charting of the primate retina utilizing Granit's electrophysiologic technics, as previously employed in the study of other mammalian retinas; (3) further research on the effects of prolonged exposure to monochromatic light leading to selective laminar degeneration, and (4) a detailed analysis of further clinical cases with color scotomas or color blindness.

Prof. W. E. L. Clark, Prof. S. Polyak and Prof. H. Klüver offered a critical discussion of the subject and gave help in the preparation of this paper.

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RHEUMATOID INVOLVEMENT OF THE EXTRAOCULAR MUSCLES

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THE DIAGNOSIS of rheumatic disease of the eyes was made with great frequency in the past. It has slowly been relegated to obscurity as more specific etiologic factors in disease have been uncovered. At present, it represents a "wastebasket" diagnosis, hard to substantiate and made only infrequently, and the etiology is unknown.

The association of inflammation of the episclera and sclera with diseases of the articular structures of the body was reported by Hutchinson [1] in 1885, by Fuchs [2] in 1895 and by Wangenmann [3] in 1897. Verhoeff and King [4] reported a case of a perforating scleral lesion associated with rheumatoid arthritis; these authors discussed similarly reported cases of a condition designated as scleromalacia perforans. Smoleroff [5] reported 3 cases of advanced rheumatoid arthritis and scleral nodules; the pathologic changes were deep abscesses in the sclera.

Kneis [6] referred to rheumatism as the etiologic factor in iritis, cyclitis, tenonitis, keratitis, optic neuritis and rheumatic paralysis. Fuchs mentioned rheumatism frequently as an etiologic factor in sclerosing keratitis, scleritis posterior, iritis and tenonitis. Of the last condition, he stated: "The causes of tenonitis are still obscure; one makes gout, rheumatism and exposure to cold responsible as etiologic factors." The disease tends to recur and does not leave behind any permanent results.

Babel [7] reported histologic changes in the eye in a man aged 35 who died of rheumatic myositis. There was involvement not only of

1. Hutchinson, J.: Tr. Ophth. Soc. United Kingdom **5**:1, 1885.

2. Fuchs, E.: Diseases of the Eye, authorized translation by E. V. L. Brown from fifteenth German edition of "Lehrbuch der Augenheilkunde," Philadelphia, J. P. Lippincott Company, 1932, p. 197.

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6. Kneis, M.: Relations of Diseases of the Eye to General Diseases, New York, W. Wood & Company, 1895, p. 372.

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the sclera, Tenon's capsule and uvea, but also of the external muscles of the eye, which showed a characteristic myositis with nodules. The same changes were noted in the myocardium, endocardium and synovial membranes. In a series of 105 cases of rheumatic fever carefully studied by Rudolph, no ocular abnormalities were found.

The case to be reported is one in which there was intimate association of recurrent ocular inflammation with generalized bouts of a rheumatoid syndrome.

REPORT OF A CASE

First Attack.—B. B., a white girl, was first observed in November 1940, at the age of 9 years. At that time she complained of severe headaches over the left eye. Diplopia followed two weeks later; the left eye was completely immobile in its excursions and was fixed in the primary position. The eyeball was white, with no apparent inflammatory process of the anterior portion of the sclera or episclera. There was no exophthalmos. Over a period of ten weeks the pain and diplopia disappeared.

Second Attack (November 1941).—Right Eye: The patient had been free from symptoms for one year, when the right eye became involved. There were some

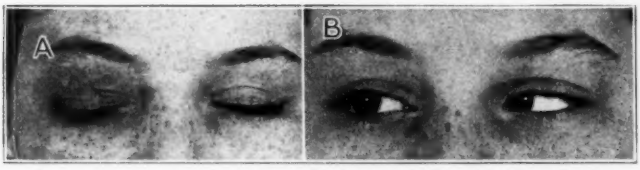

Fig. 1.—(*A*) Proptosis and edema of the upper lid and (*B*) poor abduction of the right eye during the second attack.

edema of the upper lid, slight chemosis and proptosis and mild pain (fig. 1 *A*). Diplopia was present and increased on her looking into the field of the right lateral rectus muscle; the diplopia was not due to refusal to use this muscle because of pain. The ocular excursions were normal except for poor abduction of the right eye (fig. 1 *B*). On the Hertel exophthalmometer, the right eye measured 18 mm. and the left eye 15 mm. The edema of the lid, as well as the chemosis, pain and exophthalmos, disappeared rapidly. However, the diplopia remained the most prominent feature. As time progressed, the superior oblique, the medial rectus and then the superior rectus muscle became involved in that order, with diplopia increasing in the field of each muscle as it became affected.

The temperature ranged about 100 to 101 F. for four weeks. The sedimentation time was considerably increased, measuring 24 mm. in thirty minutes. Erythema nodosum was present for two weeks, associated with migratory polyarthritis (fig. 2). The electrocardiogram was normal. Escherichia coli was cultured from the urine. A patch test gave a negative reaction to tuberculin. Examination of a peripheral blood smear revealed mild leukocytosis, with 15,000 white cells, 74 per cent of which which were polymorphonuclear leukocytes and 26 per cent lymphocytes.

The patient made a gradual recovery over a period of eight weeks. She was completely free of diplopia and all other symptoms until July 1942.

Third Attack (July 1942).—Right Eye: The right eye was then involved, with diplopia the most prominent feature and with some edema and pain. This episode lasted six weeks.

Fourth Attack (January 1943).—Left Eye: The patient was free from symptoms between attacks. This episode involved the left eye and necessitated hospitalization for four weeks.

Fifth Attack (July 1943).—Left Eye: After an interim of six months, during which the patient was free of diplopia and all symptoms, the left eye became involved with diplopia and some pain. Massive doses of thiamine hydrochloride were given, without apparent effect.

Sixth Attack (July 1945).—Left Eye: Until this episode, the patient had been free of symptoms for two years. There was mild edema of the upper and lower lids of the left eye, accompanied with severe pain. Visual acuity was 20/20 in

Fig. 2.—Erythema nodosum.

each eye with correction. Marked tenderness was present on palpation over the orbital rim in the region of the trochlea of the superior oblique and over the periosteal attachments of the inferior oblique. Diplopia was present in the fields of action of these two muscles. The fundi were normal. During the first two weeks of this attack, the pain subsided, but the diplopia kept increasing in the fields of the oblique muscles. Fulness appeared in the lower lid, and a mass could be felt in the region of the periosteal attachment of the inferior oblique as the patient looked upward; this was thought to be a swollen inferior oblique muscle. With the Hertel exophthalmometer, the left eye measured 16 mm. and the right eye 14 mm. of exophthalmos. There were no abnormalities of the visual fields. The intraocular pressure was normal. Clinically, the paranasal sinuses were free of any pathologic condition. Roentgenographic examination of the skull and sinuses failed to reveal any abnormalities. The optic foramens were within normal limits of size and form. General physical examination revealed nothing abnormal. Cutaneous tests showed that the patient was allergic to chestnuts, walnuts, apricots,

pumpkin and hog's hair. The temperature ranged around 98 F., and there was no elevation of the pulse rate. Examination of the blood revealed 4,200,000 red cells, with 13.3 Gm. of hemoglobin per hundred cubic centimeters and 7,000 white cells, 52 per cent of which were polymorphonuclear leukocytes, 44 per cent lymphocytes and 4 per cent monocytes. The basal metabolic rate was —14 per cent. Intramuscular administration of large doses of penicillin was apparently without response. The diplopia slowly decreased over a period of eight weeks.

Seventh Attack (Oct. 1, 1945).—Right Eye: The patient was free from symptoms and without diplopia for four weeks, when the right eye became affected. There was mild edema of the upper lid (fig. 3). During this episode the superior oblique and then the superior rectus muscles were involved, with pain on looking into the field of each muscle and tenderness to palpation of the globe over the affected muscle. As involvement of these two muscles subsided, the medial rectus muscle became affected.

Two weeks after the onset of this episode, one could palpate several tender subcutaneous nodules in the scalp in the occipital region. It was found that the muscles of the back of the neck were tender. A transitory period of migratory polyarthritis involved the right ankle, both wrists and the metacarpophalangeal

Fig. 3.—Edema of the upper lid of the right eye and paresis of the internal rectus muscle during the seventh attack.

joints of the right hand. These joints were red, hot, swollen and painful to movement and palpation. Erythema nodosum was present for four days. The temperature ranged from 98 to 101 F. The peripheral blood smear was normal, with no eosinophilia. Biopsy of an excised subcutaneous nodule from the scalp revealed nonspecific fibrosis.

Subsequent Course.—During 1946 there were occasional transitory episodes of diplopia associated with migratory polyarthritis. On Feb. 2, 1946, paresis of the left superior rectus muscle was noted. This subsided rapidly, and on Feb. 13, 1946 the left inferior rectus muscle was found to be paretic. No sooner had the diplopia been overcome than the left inferior oblique was found to have been affected (fig. 4). In July 1946 there was spontaneous diplopia in the position of eyes left beyond the midline and in the lower fields below 30 degrees. Paresis of the right superior oblique could be mapped out with the cover test (fig. 5 *A*). Diplopia disappeared gradually over a period of four weeks. At the last examination, on Jan. 3, 1947, no diplopia could be elicited with the red glass test; only traces of hyperphoria were present (fig. 5 *B*). Except for pronounced fatigue, the patient was free of complaint. During 1947 and 1948, the patient resided in Southern California and had no attacks.

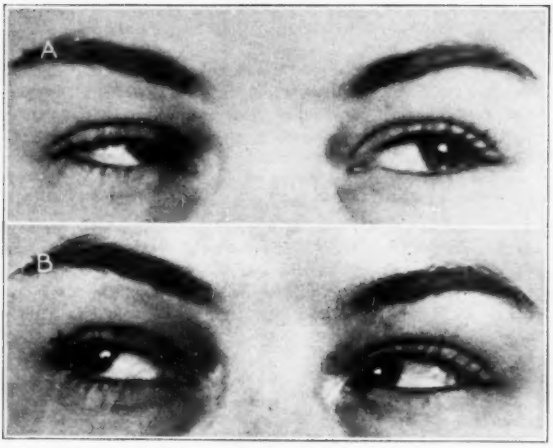

Fig. 4.—*A*, paresis of the left superior rectus; *B*, paresis of the left inferior oblique.

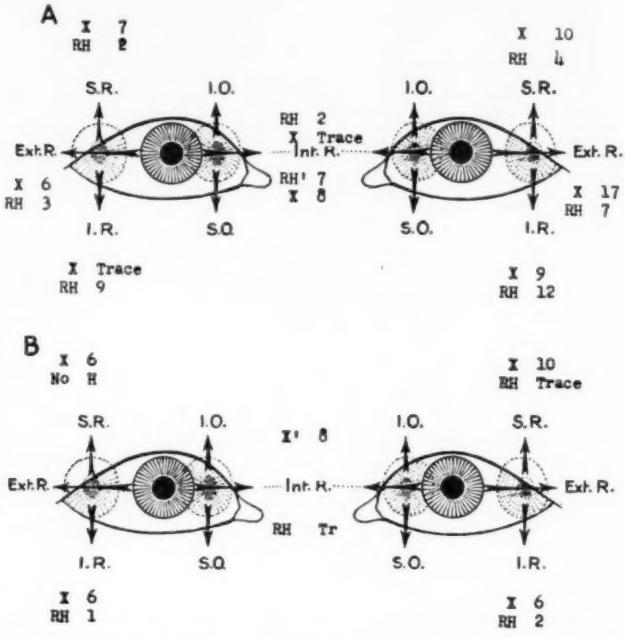

Fig. 5.—*A* (July 26, 1946), spontaneous diplopia to the left and beyond the midline in the lower fields; paresis of the right superior oblique muscle. *B* (Jan. 3, 1947), no diplopia as tested with the red glass. Paresis of the right superior oblique muscle has subsided. Charting was done on the diagnostic card designed by Dr. J. W. White, New York.

COMMENT

The most prominent feature in this case was diplopia. During an acute attack double vision could be mapped out, the diplopia being due to paresis of individual muscles and increasing in the field of action of the particular muscle. There was pain on looking into the field of the paretic muscle, with tenderness to palpation over it. Without question, Tenon's capsule was involved in several episodes, as manifested by the exophthalmos, edema of the lids, chemosis and pain. However, the involvement of the external ocular muscles appears to have been the most prominent feature and is of interest from the point of view of complete remissions and the ability to overcome the diplopia by fusion. There was repeated association of ocular involvement with migratory polyarthritis, erythema nodosum, fever, rapid sedimentation time and subcutaneous nodules. It appears that the extraocular muscles were affected by a transitory inflammatory process, the cause of which was the same as that producing the generalized rheumatoid syndrome.

SUMMARY

A case is reported of repeated episodes of diplopia with remissions in which the diplopia was overcome by fusion.

These episodes were associated with a generalized rheumatoid picture.

The ocular involvement was probably on a rheumatoid basis.

The repeated inflammatory process of the extraocular muscles was the most prominent feature of the ocular picture.

INFLUENCE OF IONTOPHORESIS ON THE PERMEABILITY OF THE EXCISED CORNEA

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IONTOPHORESIS of therapeutic agents capable of ionization has been shown to give high intraocular concentrations of these substances. Since the epithelium of the excised cornea not only is virtually impermeable to electrolytes [1] but also possesses a high degree of electrical resistance,[2] the undamaged cornea would seem to be unsuited to the iontophoretic transfer of ions.

The appearance of a transient epithelial haze after the use of iontophoresis has been noted by several investigators.[3] This is usually reported as clearing within a few hours, but in 1 case a 4 mm. nebula persisted three weeks after treatment.[3a] These observations considered with the finding that damage to the corneal epithelium increases its permeability to penicillin [4] lead one to suspect that the reported efficacy of iontophoresis may be due to epithelial injury. Von Sallmann clearly demonstrated by in vivo experiments that the iontophoretic transfer of penicillin into and through the corneas of rabbits was accomplished by a depressant effect of current flow on the barrier properties of the epithelium, by ionic transfer and, to a slight degree, by diffusion.[5]

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This paper has been accepted in completion of requirements for the Diploma in Ophthalmology of McGill University, Montreal, Canada

1. Cogan, D. G., and Kinsey, V. E.: The Cornea: I. Transfer of Water and Sodium Chloride by Osmosis and Diffusion Through the Excised Cornea, Arch. Ophth. **27**:466-476 (March) 1942.

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At the suggestion of Dr. David Cogan, director of the Howe Laboratory of Ophthalmology, the following investigation was undertaken to determine whether the procedure of iontophoresis is capable per se of altering the barrier properties of the excised cornea. This tissue is especially suitable for such studies, as Cogan and Kinsey have pointed out,[1] because of its maintained functional integrity after the death of the animal.

PROCEDURE

The permeability of the excised beef cornea was studied with and without iontophoresis. The procedure, modeled after that of Cogan, Hirsch and Kinsey,[6] consisted of tying excised corneas over the ends of glass tubes and placing within the tubes solutions of test substances. The lower, cornea-bearing ends of the tubes were then immersed in solutions initially free of test substances. In this manner, the penetrability of a test agent could be determined after any given time by assay of the material in the lower solution.

The tubes employed were made from Pyrex test tubes with inside diameters of 9 mm., which were converted into open tubes by removal of the rounded bottoms. The cross sectional area of these tubes was approximately 75 sq. mm.

Three kinds of test substances were selected for study: a cation, magnesium; an anion, chloride, and an essentially nondissociative substance, levulose. Magnesium was in the form of magnesium sulfate, and chloride, of sodium chloride.

The volume of the solutions containing the test substances was 2 cc. for the chloride and levulose investigations and 3 cc. for the magnesium studies. The volume of the solution in the container in which the cornea was immersed was 5 cc.

Determination of magnesium and levulose was performed colorimetrically, using the methods of Gillam[7] and Corcoran and Page,[8] respectively. Chloride was determined by titration with mercuric nitrate, as outlined by Schales and Schales.[9] The results for chloride determinations were corrected for blanks obtained from similar experiments when no additional chloride was present in the tubes. Similar blanks for levulose and magnesium gave zero readings.

Beef corneas from freshly killed animals were excised whole or after the removal of the epithelium in certain instances. These corneas were tied securely over the flared ends of the test tubes with the outer, or epithelial, side toward the lumen. It has been shown that it is difficult to obtain whole corneas without some damage to the endothelium.[10] Accordingly, to eliminate a possible

6. Cogan, D. G.; Hirsch, E. O., and Kinsey, V. E.: The Cornea: VI. Permeability Characteristics of Excised Cornea, Arch Ophth. **31**:408-412 (May) 1944.

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10. Cogan and Kinsey.[1] Leber, T.: Studien über den Flüssigkeitwechsel im Auge, Arch. f. Ophth. (pt. 2) **19**:87-186, 1873.

variable of mechanical endothelial damage, the endothelium was removed completely in all instances by rubbing this surface with a cloth.

Preliminary experiments with iontophoresis in unbuffered solutions revealed decided shifts in p_H values, presumably due to electrolysis of the sodium chloride derived from the cornea. To eliminate any effect of strongly acid or alkaline solutions on epithelial permeability, all solutions were therefore buffered. The p_H was adjusted initially to approximately 7.0 for the chloride and levulose investigations, and 7.6 for magnesium determinations. Two-tenths molar phosphate buffer solution was used for the chloride and levulose studies, and one-tenth molar barbital-hydrochloric acid buffer solution for the magnesium studies. These buffers limited the shift in hydrogen ion concentration to 1.0 or less p_H units. Direct observation during iontophoresis when colorimetric indicators were in the solutions showed no evidence of localized changes in p_H at the corneal surfaces.

The corneas which were subjected to iontophoresis were stationed in groups of six with platinum wire electrodes so placed that the corneas were in electrical series. This arrangement insured that each cornea was subjected to the same current. Care was taken that the electrodes were not in direct contact with the corneal surfaces. Strength of current was set arbitrarily at 2

TABLE 1.—*Transfer Through Corneas With and Without Epithelium (No Iontophoresis)*

Substance	Epithelium Intact	Epithelium Removed
Magnesium	0.00 mg.	0.49 mg.
Chloride	0.20 mg.	8.5 mg.
Levulose	0.07 mg.	3.7 mg.

milliamperes in all instances and was derived from a 110 volt direct current line, with 29,000 ohms of fixed resistance, 25,000 ohms of variable resistance and a milliammeter interposed. The standard period of iontophoresis was sixty minutes, an interval which permitted reasonably accurate quantitative estimation of the test materials.

The barrier properties of the epithelium to the test substances were determined (*a*) before iontophoresis, (*b*) during iontophoresis and (*c*) after iontophoresis, and a minimum of 6 corneas was used for each determination. All results are written as averages.

RESULTS

Before Iontophoresis.—Table 1 shows the amounts of test substances which passed through corneas with intact epithelium and the amounts which passed through corneas from which the epithelium had been removed. In these experiments, the test substances were present for sixty minutes in 5 per cent solution, and no iontophoresis was employed at any time.

During Iontophoresis.—Table 2 shows the amounts of test substances which passed through corneas during sixty minutes of iontophoresis when the anode was on the epithelial side. It also shows the amounts passing through a similar number of control corneas tested simultaneously but not subjected to iontophoresis. The latter group

is analogous to that shown in column 1 of table 1. Test substances were again present in 5 per cent solution, and the corneal epithelium was present in all cases.

Table 3 shows the results obtained in a similar experiment but with current polarity reversed for the period of iontophoresis.

TABLE 2.—*Transfer Through Intact Cornea With and Without Iontophoresis (Anode on Epithelial Side)*

Substance	With Iontophoresis	Without Iontophoresis
Magnesium	0.19 mg.	0.00 mg.
Chloride	0.00 mg.	0.16 mg.
Levulose	0.74 mg.	0.05 mg.

TABLE 3.—*Transfer Through Intact Cornea With and Without Iontophoresis (Cathode on Epithelial Side)*

Substance	With Iontophoresis	Without Iontophoresis
Magnesium	0.00 mg.	0.00 mg.
Chloride	1.6 mg.	0.4 mg.
Levulose	0.02 mg.	0.05 mg.

TABLE 4.—*Transfer Through Intact Cornea with Iontophoresis Preceding Introduction of Test Substance (Anode on Epithelial Side) and Also Through Intact Cornea Without Iontophoresis*

Substance	With Iontophoresis	Without Iontophoresis
Magnesium	0.02 mg.	0.00 mg.
Chloride	0.57 mg.	0.24 mg.
Levulose	0.26 mg.	0.04 mg.

TABLE 5.—*Transfer Through Intact Cornea with Iontophoresis Preceding Introduction of Test Substance (Cathode on Epithelial Side) and Also Through Intact Cornea Without Iontophoresis*

Substance	With Iontophoresis	Without Iontophoresis
Magnesium	0.04 mg.	0.00 mg.
Chloride	0.56 mg.	0.26 mg.
Levulose	0.35 mg.	0.09 mg.

After Iontophoresis.—Table 4 shows the amounts of test substances which passed through corneas when iontophoresis preceded the introduction of the substances. In the experiments which are represented in this table, the anode was on the epithelial side of the cornea. Corneas were first subjected to iontophoresis with only buffer solutions on each side of the corneas. After the period of iontophoresis, sufficient test substance was added to the solution in the tube to give a final concentration of 5 per cent solution of that substance. This solution

was allowed to remain above the corneal epithelium for sixty minutes, without iontophoresis. A similar number of control corneas were treated identically except that they were not subjected to iontophoresis at any time.

Table 5 shows the results obtained in a similar experiment but with current polarity reversed for the period of iontophoresis.

Gross examination showed that all corneas subjected to iontophoresis had a diffuse epithelial haze after the procedure. It is interesting to note, however, that when these corneas were sectioned and stained the histologic counterpart of the epithelial haze was not capable of identification.

COMMENT

The results of experiments demonstrating permeability with and without the corneal epithelium (table 1) accord with previous observations which showed that the epithelium of the excised cornea is an effective barrier to substances of the nature of the test agents employed.

With iontophoresis in the presence of these substances, the penetration of magnesium and chloride ions through the cornea increased in a manner predictable on the basis of electrical attractions. Thus, the anions passed through the cornea toward the anode and the cations toward the cathode.

It is noteworthy that levulose, having p_K's of 11.68 and 13.24, penetrated the cornea to a much greater degree when the anode was on the epithelial side than when the polarity was reversed. No explanation for this phenomenon is apparent.

In the third group of experiments (tables 4 and 5), in which iontophoresis preceded the introduction of the test substances, it was observed that the penetration of these substances was greater than penetration through control corneas not subjected to iontophoresis. Moreover, the penetration was greater when the iontophoresis, with polarity favoring in the instances of magnesium and chloride, was performed in the presence of the test substances than when it was performed before the addition of these substances.

On the basis of these findings, it seems reasonable to conclude that the barrier properties of the epithelium are impaired by the iontophoretic procedure. This change in permeability does not appear to depend on the changes in the hydrogen ion concentration in the buffered solutions employed. The impaired permeability thus would seem not only to permit the ions to move by diffusional processes due to their kinetic motion, but, in the presence of continued iontophoresis, to enable them to cross, at an accelerated pace, a previously nonconducting barrier. This barrier, in the absence of damage, is presumably resistant to the passage of ions, even with the aid of an iontophoretic current.

SUMMARY AND CONCLUSION

Iontophoresis increases the permeability of the epithelium of the excised cornea to magnesium, chloride and levulose.

It is concluded that this alteration in epithelial permeability is of major importance in obtaining the high intraocular levels which have been achieved by iontophoresis.

The staff members of the Howe Laboratory of Ophthalmology gave assistance and guidance in the execution of this work.

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TRACHOMA IN MISSOURI

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HISTORICAL REVIEW

TRACHOMA is one of the oldest diseases known to man. Well known since Biblical times, it is still one of the greatest causes of blindness in the world. Among the ancient Romans and Greeks, such famous men as Aetius, Paulus Aeginetus, Alexander, Trailaus, Horace and Cicero were said to have been victims. It was known in ancient Egypt, and from the evidence of papyri and of crude instruments used for grattage and for trichiasis, one can assume knowledge of its ravages back to the nineteenth century B. C. India and Egypt are recognized as the "cradles of trachoma." It was known in ancient Greece, as is evidenced in the writings of Hippocrates, in the fifth century B. C. In 14 A. D. Celsus gave a good clinical description of the roughness of the lids and treatment by rubbing and scarification. Galen (131-201 A. D.), who practiced in Asia Minor, as well as in Egypt and Rome, mentioned various remedies for trachoma in numerous places in his writings. The Roman classical writers, including Pliny (23-79 A. D.), Marcellus (380 A. D.) and Cassius (447 A. D.), were evidently acquainted with its clinical manifestations. In medieval manuals, Greek and Arab surgeons gave lucid descriptions of its natural history and became adept at dealing with it. Shakespeare probably makes reference to this disease when he quotes Lancelot as saying that his father "was more blind than sand blind, he was gravel blind."

From time immemorial, trachoma has existed in Europe as an endemic disease, having been imported from its natural habitat in the Middle East by crusaders returning from Palestine. However, it was Napoleon's army that was deemed responsible for the general spread of the disease. When Napoleon invaded Egypt (1798), so many of his troops became infected with a purulent ocular disease that he was forced to return to the European continent. The disease became endemic in Europe and invaded England. One historian ascribes the loss of the battle of Waterloo to the prevalence of trachoma among the French troops. Trachoma was also known at that time as military

From the Missouri Trachoma Hospital.
Read before the St. Louis Ophthalmic Society, April 2, 1948.

ophthalmia, and it spread rapidly throughout Europe, with devastating results, via the armies that overran the Continent during that period (1801-1820). The civilian population became infected in the wake of the military. When troops were disbanded and returned to their homes, they spread trachoma among their families.

In southern Europe, trachoma spread gradually over practically all of the continent and is still prevalent in southern European countries. England at one time had a very high percentage of trachoma, but the government established schools in which all children with trachoma were compelled to enter and remain until the disease was completely arrested. By this method, trachoma in England has been almost completely eradicated. At the present time it is epidemic in Egypt, China, Japan, India, Palestine, Iraq, Iran, North Africa and Russia. It is prevalent in Egypt in over 90 per cent of the population and is known there as Egyptian ophthalmia. In the United States, it is endemic in Missouri, Tennessee, Kentucky, Arkansas, Oklahoma, southern Illinois and West Virginia. Sporadic cases have been found in many other states.

To the best of our knowledge, trachoma was introduced into the United States during Colonial days by the early settlers from England and the Continent. Later, as a result of the increased prevalence throughout Europe following the Napoleonic wars, infection in America became more widespread with the influx of settlers from the British Isles. Duke-Elder [1] stated that trachoma in England is an alien disease, imported, propagated and passed to the native population by aliens. This may be a true statement, but it should be noted that the early English settlers were responsible to a large extent for bringing the infection to America and spreading it westward from the coastal settlements.

Trachoma was found first among the mountaineers of Tennessee, Kentucky and West Virginia. As emigration moved westward, these mountaineers carried their infection with them and spread it among the settlements. The southern half of Missouri and the northern half of Arkansas were settled to a great extent by immigrants from Tennessee and Kentucky. Although the most widespread infection is in the counties south of the Missouri River, there is not a county in the state that does not have a certain amount of trachoma (figure), spread by migratory laborers. During the recent war years, migration of families within the state and from state to state has tended to disseminate the disease.

Most of the Indian tribes of the United States are infected with trachoma, the percentage varying from 1 to 20. Whether or not trachoma was present among the Indians at the time of Columbus'

1. Duke-Elder, S.: Text-Book of Ophthalmology, C. V. Mosby Company, 1946, vol. 2, pp. 1595-1596.

discovery is not accurately known. Fox,[2] after consulting more than thirty authoritative Indian works, as well as having personal communications with missionaries and other competent observers, reported that from time to time there have occurred among Indians pronounced epidemics of an ocular disease, epidemics that spread with great rapidity through the tribes and then subsided. He made reference to a kind

Distribution by counties (Missouri) of patients hospitalized at Rolla (total to 1948, 6,649) and of pensioners blind from trachoma (total to 1945, 1,259). The former are represented by dots; the latter, by asterisks.

of grattage performed by the medicine men of several of the tribes, in which they used an improvised scraping instrument, made by sharpening one edge of a reed.

2. Fox, L. W.: The Trachoma Problem Among the North American Indians, J. A. M. A. **86**:404 (Feb. 6) 1926.

In 1897 immigrants with trachoma were debarred from entering the United States. This has been largely efficacious in preventing the entry of foreign sources of infection. After World War II the American soldiers who returned from overseas duty were given rigid ophthalmologic examinations on discharge from the service, so that little foreign infection has been added to the population. The high standard of sanitation among the American armed forces has also been a factor in keeping the spread of this infection at a minimum.

Today, trachoma is probably the most widespread infectious disease of the eyes in the world, and is responsible for a greater percentage of blindness than any other one disease of the eye.

THE MISSOURI TRACHOMA HOSPITAL

The Missouri Trachoma Hospital is a state-owned and state-managed institution, having for its main purpose the treatment and eradication of trachoma within the state. The initial program was inaugurated by the United States Public Health Service, the facilities being available to victims of trachoma from adjoining states.

In the early twenties, the service began to concentrate in the Ozark region of southern Missouri, although still under federal management.[3] A mobile railroad car was supplied by the St. Louis–San Francisco Railroad Company for the purpose of housing and transporting the complete equipment and personnel of the trachoma service group. This car ran over the regular company tracks and contacted many towns throughout the state. It contained a complete clinic for registering and examining patients and for treating them on the spot. In many cases the necessary surgical treatment was performed in an operating room within the car.

Although this method of service covered a wide area, it lacked many of the advantages of being located in a permanent place, particularly with reference to hospitalization of patients with active medical and surgical trachoma. In 1923 the trachoma service came to Rolla and established itself in a wooden frame house on Elm Street. This was the first permanent location in Missouri. The frame dwelling served as an outpatient clinic and hospital and also provided quarters for the medical and other personnel. Patients with active and complicated disease were admitted and were kept under observation and treatment until their condition was improved or the process arrested. Surgical patients were encouraged to remain after operation until well healed. Experience had shown that patients with trachoma prematurely discharged after operation tended to have recurrences.

3. The service was under the supervision of Dr. John McMullen, United States Public Health Service.

Many learned of the nature of the hospital, and letters and inquiries began to reach the office in regard to the type of service offered and the method of entering the hospital. Thus, the permanent nucleus for the present Trachoma Hospital was established.

As the years passed, the reputation of the hospital spread, and the people throughout the state began to associate Rolla with the trachoma service. During the early thirties, the ophthalmologists of St. Louis and Kansas City took an active interest in the little hospital at Rolla, and many visited it. These men encouraged the work that was being done and spread the word among their colleagues.

In 1934 the United States Public Health Service relinquished control of the Trachoma Hospital to the state of Missouri. Since that time the Missouri State Division of Health has supervised the service, its policies and its public relations.

As more and more citizens of the state became aware of the hospital and its program, and learned of and used its services, a need for a greater and more modern institution was felt. Therefore, in 1939, a new site was chosen at the outskirts of Rolla, and a modern concrete building was erected, with a patient capacity of fifty-five beds and quarters for four nurses. The main building includes administrative offices, dining rooms, a large modern operating room and sterilization room and additional space for laboratory facilities and conference rooms. A craft shop and playground have recently been provided for recreational activities. In addition to the regular hospital facilities, there is an outpatient service clinic, which cares for the needs of patients arriving from day to day for examination and diagnosis. Patients whose ocular conditions are not severe enough to warrant hospitalization are given eye drops for treatment at home and advised to return for reexamination at a later date. The patients with a severer condition are admitted to the hospital for intensive medical or surgical care. Bed and board, medical care and laundry are all furnished free; only transportation to and from the hospital is not provided. There is no restriction as to age, sex or economic status.

As a part of the general program for the eradication of trachoma within the state, field clinics are held at various county centers. These are primarily diagnostic and consultative. Some treatment, in the way of drops for home use, is dispensed. Newly found patients with active trachoma, as well as old patients who have had recurrences, are encouraged to enter the hospital for intensive treatment.

In addition to the necessary medical and surgical treatment of the eyes, the general welfare of the patient is not neglected. The hospitalized patient is given a well balanced and highly nourishing diet, supplemented with vitamin therapy when indicated. By precept and example, the patient is taught proper sanitary and hygienic living, and personal habits of cleanliness are emphasized. Thus, a majority of the patients

with arrested disease are returned to their homes in improved general health, with a higher regard for personal welfare and with instructions concerning the means of avoiding reinfection.

TRACHOMA

The word trachoma is taken from the Greek, *τράχωμα*, and its meaning is "rough." The name is well chosen, as the infection is primarily an inflammation of the tarsal conjunctiva of the eyelids, causing a roughened appearance of this membrane. It is also called popularly "granulated lids." It is a chronic, nonsuppurative disease of the palpebral, bulbar and corneal conjunctivas. The disease is not of bacterial origin; in the light of present knowledge, it is believed to be caused by a virus, or minute elementary (inclusion) bodies too small to be visualized by ordinary microscopes. Pus, when present, is due to a secondary invader. Infection may occur from transfer of the secretion by means of towels, washcloths, bed linen, pillows, clothing, handkerchiefs or other articles which may be brought into contact with the eyes, or by personal contact. Most important is the factor of intimate contact with a trachoma-infected person. The infectivity of trachoma is not high. It is the constant, intimate exposure over a period of weeks or months that accounts for its spread from one person to another. For this reason, families or groups living in close contact will more readily acquire the disease. Trachoma is not readily acquired by handling door knobs, pencils, eating utensils or institutional fixtures, although contact with such contaminated articles daily may enhance possibility of infection.

Because of overcrowding, trachoma is found more frequently among poor families. Their homes consist of rude dwellings. As a rule, the water supply is limited, being obtained either from a dilapidated well or a spring at some distance from the dwelling. Linen supplies and toilet articles in such homes are very limited; for instance, the family towel is commonly used by all members of the household. It is also usual for such families to have a common washbowl, in which all members wash their faces and hands, without changing the water.

Although the poor are more likely to acquire the disease, for the reasons just stated, it may also attack persons of education and higher financial standing. For example, during recent years, my associates and I have had among our patients at the hospital a doctor's son, a lawyer, several engineers, postal clerks, several clergymen, many business men and college students.

At present, trachoma is essentially a rural disease in Missouri. It is becoming increasingly rare in large cities. The vast majority of patients who attend the Trachoma Hospital come from communities with a population of less than 1,000, and a great many come from small hamlets, or even from thinly settled regions situated miles from a

highway. Only about 10 to 20 per cent of the patient census is made up of urban residents. Mossman [4] attributed the low rate in cities to the easy accessibility of oculists and to better living conditions.

Certain races are more susceptible than others; yet no one is immune except the Negro. Full-blooded Negroes do not acquire this disease, but persons of diluted racial strains may become infected. When the latter acquire trachoma, the course of the disease is always mild. By contrast, from my personal observation, it can be said that among the native Nordic white persons of Missouri the disease manifests a striking virulence and produces highly distressing symptoms, and it results frequently in irreparable complications. The conjunctivitis, when fully developed, is acute, painful and depressing, with intense photophobia and swollen lids. The patient presents a truly pitiable picture and is usually immobilized by his affliction, necessitating hospital treatment. The advanced complications of corneal ulceration, with perforation, severe blepharospasm, intense photophobia (even in a shaded room), edema of the conjunctiva and a proliferative pannus with cicatrization and symblepharon—these form the picture commonly seen in persons with advanced trachoma in Missouri.

On the other hand, trachoma among the inhabitants of the Middle East does not exhibit such virulence or produce such a devastating picture. Wilson [5] stated that trachoma among Egyptians tends toward spontaneous cure more frequently than among Europeans. He observed further that some of the Egyptians suffer little from this disease and that the lesions are mild, in contrast to the severity of the lesions among Europeans. Wilson stated the belief that this is not due to attenuation of the virus, because when Egyptian trachoma passes to the conjunctiva of an Englishman it produces severe, distressing symptoms and much suffering.

In my opinion, some degree of racial immunity exists among the French and Italian descendants living in Missouri. Many of these people reside in the trachoma areas of Missouri and are exposed to this infection under the same conditions as are other native white persons; yet when such patients are infected with trachoma, they exhibit only the milder symptoms, with moderate scarring of the eyelids, little or no involvement of the cornea and insignificant pannus that involves little or no visual loss. Although other factors may be concerned, this is undoubtedly due to inherent racial immunity. For example, the Italians of Rosati (a community producing wine and grapes, 100 miles [160 kilometers] southwest of St. Louis) live together in a settlement

4. Mossman, P. D.: Present Status of the Trachoma Situation in the United States, Eye, Ear, Nose & Throat Monthly **9**:430-435 (Nov.) 1930.

5. Wilson, R. P.: Trachoma: A Selection of Personal Observations and Experiences, Giza Memorial Ophthalmic Laboratory 14th Report, 1939-1944, pp. 24-25.

of their own, in a county (Phelps) where the incidence of trachoma is high (figure). These people attend the same schools, have commerce with neighboring people and intermarry freely with the non-Latin races of their communities, so that the exposure factor and standards of living are comparable to those of the surrounding peoples. The same is true of French descendants in Washington County (Potosi), Ste. Genevieve County and the Cape Girardeau area, where the incidence of trachoma is high. In contrast, the Anglican and Germanic white descendants living in the same areas are far more likely to have the disease in its severest forms.

Green [6] suggested that the heavily pigmented eye may have more inherent immunity to the trachoma virus than the more lightly pigmented eye. This concept would explain the reason that trachoma exhibits such virulence and destruction of tissue in the Nordic European, and that the disease provokes a milder response among Southern Europeans, Mediterranean peoples and the Indians of North America and of Asia. This, furthermore, would account for the apparent immunity of the Negro. It should be stated, however, that in a large percentage of native Missourians of both Nordic and non-Nordic extraction having dark brown irises and deep pigmentation some of the worst ravages of this disease develop.

In trachoma there is practically no acquired immunity. Once a patient has had the disease and has then recovered, he may still suffer another attack at some later date. The second or third recurrence may be even worse than the original attack, and may occur even after a fairly long period of quiescence. Patients who have had few and mild complications and who have escaped without serious damage to vision seem to be more liable to recurrences. Patients with stubborn disease with many complications which finally become arrested are, in my opinion, less likely to have recurrences. It is possible, therefore, that some individually acquired immunity may develop, although, unfortunately, only after the disease has first taken its toll on the eye of the sufferer.

Climatic conditions are predisposing factors to some extent, the southern or warm climates being the localities where trachoma is most prevalent. Arid lands, especially where the atmosphere is filled with dust and sand, favor the development of this disease. Thus, trachoma is highly prevalent in the southeast ("boot heel") corner of Missouri. Although predominant in the Ozark mountains, trachoma is prevalent to a considerable extent in the lowlands and in flat country. For example, one may note that trachoma is widespread in the Egyptian delta, in the Middle East, in the lowlands of the Netherlands and Belgium (following the Napoleonic wars) and, in the United States,

6. Green, John: Personal communication to the author.

in southern Illinois and in southeast Missouri (figure). On the other hand, the high Tyrol and Alpine regions of Europe are relatively free of this infection. The Prague Clinic study in 1921, after World War I, revealed that the rich agricultural district of the Elbe River was favorable to the spread of the infection, while the mountainous districts were remarkably free. Lack of sanitary conditions among the agricultural population was given as the chief factor favoring spread of the disease.

Food and vitamins [7] do not seem to play any important role in this disease. Some writers have stated the belief that inadequate diet and avitaminosis were contributory factors. Stucky,[8] who made a great contribution to the prevention of trachoma in Kentucky, was an ardent supporter of this thesis. At present this concept must be regarded as unproved.

The incidence of trachoma is not influenced by age, as the disease occurs at all ages. The greatest number of hospitalizations are of persons between 15 and 35 years of age, the next, of persons between 35 and 60 years, and the fewest, of persons 15 years old or under. These groupings conform to the occurrence of the disease in active form among patients seen in the field.

In Missouri, males are frequently affected more than females, in the ratio of about 2:1. Thus, the Trachoma Hospital was built to accommodate twice as many males as females, and this ratio between the sexes has been consistently maintained in the distribution of hospital patients. This cannot be explained by the women being more timid about submitting to an examination, since in our field and hospital clinics more females than males present themselves for examination. The reason is undoubtedly epidemiologic.

TREATMENT

Trachoma can be cured if treatment is begun in its early stages. Moderately advanced forms can often be arrested, but the patient may suffer a relapse. Advanced trachoma with scar formation and visual loss can be arrested and the eyes freed of symptoms, but rarely, if ever, is the sight restored. If the disease is left to progress year after year untreated, it generally leads to blindness.

In most cases the disease responds well to treatment [9] with sulfonamide drugs. In recent years, the tendency has been toward mild, or

7. Rice, C. E.; Sory, R.; Smith, J. E.; Faed, P. E., and Drake, A. A.: Effects of Diet and Vitamins on Trachoma, Am. J. Ophth. **17**:735 (Aug.) 1934.

8. Stucky, J. A.: Observations and Experiences with Trachoma in Eastern Kentucky, Tr. Am. Acad. Ophth. **35**:217-224, 1930; Eye, Ear, Nose & Throat Monthly **9**:455-457 (Dec.) 1930.

9. The subject of treatment is more fully discussed in a paper, "The Sulfonamide Drugs and Penicillin in Treatment of Trachoma," Am. J. Ophth., to be published.

bland, treatment in preference to the older, harsh methods. Although of time honored use, copper sulfate and silver nitrate sticks, as well as solutions of these drugs, have been abandoned at the Missouri Trachoma Hospital in favor of milder remedies. Copper sulfate and silver nitrate are caustic, irritative to the conjunctiva and devitalizing to the infected tissues; furthermore, they add to the discomfort of the patient. Moreover, the continued use of silver preparations causes staining of the conjunctiva (argyrosis), and may even increase scar formation. In their stead, the sulfonamide drugs stand as first choice because of their relative mildness of action and their apparent specificity against the trachoma virus. In my opinion, at least, trachoma responds to treatment with the sulfonamide drugs more quickly and with least injury to the affected tissues than to use of any other drug previously used. Although Wilson [10] expressed disappointment with the results of treatment of Egyptian trachoma with sulfonamide drugs, it should be pointed out that he made use of the drugs only by oral administration, and not by local instillation into the conjunctival sac. In my opinion, use of the newer, highly soluble sulfonamide drugs in solutions instilled locally into the conjunctival sac at frequent intervals is the treatment of choice. The drops have proved to be a more effective means of treatment than the tablets when the latter are given alone by mouth. It is probable that a combined method of sulfa drops instilled locally and tablets given internally may yield the best therapeutic results.

At present our treatment of choice is (1) the administration internally of sulfadiazine or combisul® [11] in 0.5 Gm. tablets, 4 to 8 tablets per day, the number depending on the patient's weight; (2) the local use of sodium sulfacetimide,[12] in 10 per cent solution, or of a similar sulfonamide compound, NU-445 [13] (gantrisin®) in 10 per cent solution, instilled into the conjunctival sac every two hours during the daytime, and (3) the application of sodium sulfacetimide ointment (10 per cent) locally between the lids for overnight. Occasionally, when a patient does not respond well to the sulfonamide treatment, he may be put on a course of silver nitrate, 0.0125 per cent solution, instilled once daily in the morning, to be followed every two hours with zinc sulfate, 0.0125 per

10. Wilson, R. P.: Trachoma: A Selection of Personal Observations and Experiences, Giza Memorial Ophthalmic Laboratory Publication, 14th Report, 1939-1944, p. 35-36; 13th Report, 1938, p. 98-99.

11. Combisul,® marketed by Schering Corporation, consists of a combination, in equal parts, of sulfadiazine, sulfathiazole and sulfamerazine.

12. Highly soluble sulfonamide compounds. Although soluble to a concentration of 30 per cent, the 10 per cent dilution was found to give optimum results in treatment of trachoma.

13. A new Hoffmann-LaRoche highly soluble sulfonamide compound not on the market, and now licensed only for experimental use. The drug is supplied in 0.5 Gm. tablets and in 10 per cent aqueous solution.

cent solution, throughout the day. This period of astringent treatment is carried out for one or two weeks, and the patient is then returned to the sulfonamide routine. Occasionally, silver nitrate 1 per cent solution, (never a stronger concentration) is applied with an applicator directly to the palpebral conjunctivas and deep into the upper and lower fornices, and immediately thereafter the conjunctival sac is flushed out with isotonic sodium chloride solution.

A new sulfonamide drug, still in its experimental stage and designated as NU-445 [13] at this writing, has been used at the Trachoma Hospital, with highly satisfactory results. It is given in the form of tablets (0.5 Gm.) by mouth and also in the form of an ophthalmic solution (10 per cent, aqueous) for local instillation. Not only is it a highly soluble form of sulfonamide compound, but it has been found to be relatively free of toxic side effects.

These procedures have been found to be most beneficial, especially in cases of early and moderately advanced trachoma, with or without pannus. Late forms, with cicatrization, entropion and corneal ulceration, are also benefited but frequently require supplementary treatment with tetracaine (pontocaine®), atropine, heat, cautery and wet dressings. If uveitis has developed, typhoid and paratyphoid vaccines U. S. P., given intravenously, have been found useful.

Surgical treatment is also indicated in cases of entropion,[14] to correct the incurvation of the eyelids; in cases of trichiasis, electrolytic epilation is useful for destruction of individual hair follicles; exuberant conjunctival growths are best handled by grattage. The tear sac may become infected, requiring extirpation; deep infection of the globe (panophthalmitis) may call for enucleation.

Important in the management of trachoma is persistent and long-continued treatment, usually many months, or even a year. On the patient's discharge from the hospital, drops are provided for home use, with the injunction that he be regular and persistent in their use. As it is a common human failing to become careless when improvement is noted and subjective symptoms are relieved, some patients do not exercise the endurance to keep up a long course of treatment. Such persons often return to the hospital with a relapse, which is usually severer than the original condition.

DIFFERENTIAL DIAGNOSIS OF TRACHOMA

There are four types of conjunctivitis which show a close resemblance: trachoma, follicular conjunctivitis, inclusion blennorrhea (commonly called swimming pool conjunctivitis) and vernal conjunctivitis (vernal catarrh).

14. Smith, J. E., and Siniscal, A. A.: Modified Ewing Operation for Cicatricial Entropion, Am. J. Ophth. **17**:382-389 (April) 1943.

Trachoma.—An early symptom of trachoma is the sensation of having a foreign body in the eye, accompanied with photophobia and lacrimation. The patient first complains of a stinging, burning sensation. If he lives on a farm, he often thinks he has a husk of wheat or a like object in his eye, but when the condition prevails he seeks help. The incubation period for trachoma is from two to three weeks, while the duration may be for life. Uncomplicated trachoma does not produce pus, which occurs only from a secondary infection.

The diagnosis is usually difficult during the early stages. There are five cardinal points to be borne in mind: (1) the presence of inclusion bodies; (2) papillary hypertrophy of the retrotarsal region of the lids, with softening of the tarsus; (3) vascularization of the cornea (pannus); (4) scarification of the conjunctiva, and (5) history of contact with a known infected person or of residence in a trachoma community.

The microscopic examination for Prowazek inclusion bodies should not be given too great importance. When the latter are found in a case of suspected trachoma, one may assume a positive and conclusive diagnosis, but failure to find these bodies does not necessarily rule out trachoma. As a rule, inclusion bodies diminish rapidly after the first several months after onset. Wilson [15] stated that inclusion bodies must be sought for at the right stage. In Egyptian trachoma he found that they rapidly decrease in number and that they are difficult to find after the disease is well established. Special training on the part of the laboratory technician is required for their detection; hence, a negative laboratory report should be taken with reservations. Consequently, more emphasis must be placed on the clinical signs, family history and contacts than on laboratory diagnosis in the individual case.

On everting the lid, one may find either the papillary or the granular type [16] of trachoma. Occasionally both types are present in the same lid. In the papillary type, the lids present a red, velvety or beefy appearance, caused by an increase in thickness of the surface of the hypertrophied conjunctiva. Often, a grayish or translucent cast is given to the palpebral conjunctiva. This papillary hypertrophy is not a distinctive characteristic of trachoma, as it may also be seen in cases of long-standing chronic catarrh, senile ectropion, encapsulated foreign body of the conjunctiva and other prolonged conjunctival inflammations. By contrast, the granular, or follicular, type is characterized by the presence of granulations (or follicles), which are really small lymph follicles formed by rounded aggregations of lymph corpuscles. These

15. Wilson,[8] pp. 16 and 26.

16. The older Fuchs classification is used here, for simplification, rather than the newer MacCallan, four stage classification.

are large, devoid of sharp outlines and deeply embedded in the conjunctival surface. As a rule, the follicles are more commonly distributed in the retrotarsal region of the upper lid. For this reason, it is highly important when one is making the examination to evert the eyelid over a suitable lid evertor,[17] so that the retrotarsal fold can be exposed and viewed thoroughly from the nasal to the temporal angle.

It is my belief, based on observations over a number of years, that the granular type of trachoma is becoming less frequent in Missouri. In former times it was fairly common to see many patients with the florid, inflammatory granules in the everted upper and lower eyelids and cul-de-sacs. Such a picture is now rare in Missouri. Today, the trachoma commonly seen is the papillary type, with the smooth, velvety, grayish or purplish conjunctiva, devoid of follicles. The granular type of inflammation is still seen occasionally in children and young adults.

If the infection has prevailed for as long as three months, one should be able to detect small vessels encroaching on the cornea, coming from above; this vascular invasion is called a pannus. This finding is absolutely diagnostic of trachoma. Trachoma can occur, nevertheless, without the presence of pannus. I cannot agree with the statement that some degree of pannus must be present in every case of trachoma.[18] In many cases a most searching examination with the slit lamp and corneal microscope will fail to show any evidence of pannus, although other cardinal signs may be clearly apparent. The explanation can only be that, while in most cases the virus attacks the conjunctiva of the lids and the cornea concurrently, there are frequent instances in which the main force of the onslaught is concentrated either in the palpebral conjunctiva or in the corneal conjunctiva (i. e., epithelium).

A pannus is not secondary or merely incidental to the roughening of the upper eyelid, or to so-called "mechanical irritation" from the lid (e. g., pannus occurs in many cases with smooth eyelids); but it is due to a specific invasion of the cornea by the virus. The resulting vascularization follows as an inflammatory defense reaction by a normally avascular tissue against the virus attack.

A true pannus cannot be positively defined as such unless short twigs or downward sprouts are present along the vessels of the upper portion of the corneal limbus. The loops of blood vessels, or "festoons," seen encroaching on the cornea at the upper portion of the limbus are not to be interpreted as true pannus; there must be present small twigs or downsprouts which arise as off-shoots from the main plexus of

17. Siniscal, A. A.: Siniscal-Smith Lid Everter, Am. J. Ophth. **28**:198-200 (Feb.) 1945.

18. Duke-Elder[1], p. 1609. Wilson, R. P.: Giza Memorial Ophthalmic Laboratory Publication, 1932, Vol. 7, p. 88.

vessels that form the circulus around the limbus. The small twigs seen in early cases may grow eventually to larger size and in time may cover the entire surface of the cornea (generalized pannus). A clear and concise summary of incipient pannus was given by Kuo [19] in his excellent paper on trachoma at the Chungking Army Hospital. Kuo laid much stress on the importance of incipient pannus and the general haziness of the lower cul-de-sac as important features in establishing an early diagnosis. With this view I heartily concur.

In the absence of pannus trachoma can be confused with vernal conjunctivitis, inclusion blennorrhea or folliculosis. In this case the diagnosis is rather difficult, and repeated observations may be necessary to establish a correct diagnosis. A history of contact (exposure) or of residence in a trachoma district is of value. In such circumstances the experienced observer will rely on other diagnostic features. For example, in trachoma hypertrophied conjunctiva tends to crack and bleed on eversion of the lid, and some of the larger follicles may rupture on pressure and extrude their gelatinous contents. Furthermore, the vessels of the upper cul-de-sac are partially or entirely covered by the overgrowth (hyperplasia) and cannot be seen. This point is of diagnostic importance in differentiating trachoma and follicular conjunctivitis, in which the vessels can easily be seen between the follicles. Another point to be borne in mind is the loss of rigidity of the tarsus; this is felt by the examiner's fingers in holding the lid when the upper lid is rolled back over a suitable lid evertor.

In the early, active stages, one will usually find the tarsus succulent and thickened; this condition, by subsequent degeneration, leads eventually to softening, cicatrization and deformation. Another important conjunctival sign is the general haziness of the lower cul-de-sac, especially at the margin of junction between the bulbar and the palpebral folds. It is seen early in the disease, frequently before pannus has developed. This is due to subconjunctival infiltration and may be present in the upper cul-de-sac to a lesser extent. Another diagnostic hint is the copious tearing that follows manipulation of the everted eyelids. The presence of white striae (cicatrices) in the retrotarsal fold is also an important diagnostic feature.

Follicular Conjunctivitis.—This condition is a follicular lymphoid hypertrophy of the conjunctiva found commonly in young adults, rarely beyond the age of 18 or 20. Without a secondary infection, the patient often does not complain of the condition. The follicles look like those of trachoma, but are smaller, more sharply limited, project farther above the conjunctival surface and occur most frequently in the lower

19. Kuo, P. K.: Incipient Pannus in Early Diagnosis of Trachoma, Am. J. Ophth. **29**:645-653 (June) 1946.

fornix. They are usually oval and arranged evenly in rows, like strings of pearls, whereas trachoma granules are round and rarely present such a regular arrangement. This disease does not lead to pannus, does not form scar tissue and usually heals spontaneously. Folliculosis does not attack the cornea, whereas as time does on trachoma attacks the cornea, causing pannus formation, ulcers and scar tissue, with subsequent loss of vision and even complete blindness.

Inclusion Blennorrhea (Paratrachoma; Swimming Pool Conjunctivitis).—This condition is also a virus disease, directly contagious, relatively harmless and only rarely accompanied with corneal ulceration. It resembles very much acute, reddened, papillary trachoma, causing considerable lacrimation and photophobia; but, in addition, it is a purulent disease. It does not form a pannus or injure the cornea. Neither does it destroy the conjunctiva, though it may be followed by fine, superficial scars. So far no method of treatment has been found adequate, although recovery may be expected in from one to six months. It occurs in the newborn, as well as in children and adults. In infants it resembles a mild attack of ophthalmia neonatorum.

Vernal Conjunctivitis.—This condition is a trachoma-simulating disease, found as a rule in young adults. It is related to summer weather, but whether to heat or light is not known. Some investigators regard it as due to allergy. The presence of eosinophils in the secretion is an important differentiating point. Symptoms are in abeyance during cold weather but become worse on the approach of spring. The warmer the season, the greater the intensity of the symptoms. The disease recurs annually for years, when it finally disappears, leaving no trace. The clinical picture of the conjunctiva remains the same, summer and winter, except that during acute periods the conjunctiva appears more injected and the eyes become reddened and watery. Constant itching and photophobia are present. The appearance of the lid on eversion is that of "cobblestone" formation on the tarsus, due to the development and proliferation of conjunctival follicles. The resemblance to trachoma is striking. However, these follicles are hard and creamy white, somewhat like cartilage. At present little or nothing is known of its causation and treatment. Such patients can be made more comfortable by cold packs, collyria containing epinephrine and camphor water and irrigations. Commonly found during the period of adolescence, it tends to disappear in adult life.

Also to be considered in a differential diagnosis are Parinaud's conjunctivitis (leptotrichosis of the conjunctiva), some fungous infections (sporotrichosis and actinomycosis), tuberculous conjunctivitis (when follicular in type), syphilitic conjunctivitis (when granular in type), acute pneumococcic conjunctivitis (in some cases) and encapsulated

foreign body in the conjunctiva. In most of the aforementioned conditions there is present some degree of preauricular or cervical lymphadenopathy, whereas in trachoma, even when the infection is attended with common secondary invaders, there is never any degree of local lymphadenopathy.

CONCLUSION

Trachoma is still one of the principal factors in the causation of blindness in the state of Missouri. Until recently it was responsible for about 16 per cent of the total known cases of blindness, and for about $250,000 per year in pensions for the blind. The incidence of trachoma in Missouri at present is on the decline. This is due to the work carried on by the Trachoma Hospital; to greater cooperation by patients, both during hospitalization and subsequently, and to earlier referral of patients by physicians and other agencies. Prior to 1926, according to the Blind Pension figures,[20] trachoma was responsible for 25.5 per cent of the cases of total blindness; from 1926 to 1935 it was responsible for only 14.4 per cent of the total blindness, and since 1935 and up to the present census figures (for 1944), for only 12.3 per cent of the total blindness. Comparable percentages for other causes of blindness in Missouri, revised to 1944, were as follows: glaucoma, 18; trauma, 12; cataract, 11, and syphilis, 8.6. However, it should be noted that these figures do not indicate rates of occurrence or of prevalence, because this roll covers only a portion of the total cases of blindness and is actually a selected list. At any rate, these figures offer proof of the effectiveness of the program for control of trachoma in the state of Missouri.

The control and eventual eradication of trachoma will depend on the discovery of all persons with trachoma and an ophthalmologic examination of all contacts and associates of persons with recognized trachoma; the treatment of infected persons at the hospital or home (depending on the severity of the infection), and, finally unremitting conformity to principles of personal and ocular hygiene on the part of the patient and his family. A rise in the economic status and general educational standards in the affected population will decidedly improve trends toward eradication of the disease in Missouri. Prevention through public health education is even more important than cure.

It is hoped that in time the disease will be entirely wiped out and that within the years to come it will be remembered only as an extinct clinical entity.

Missouri Trachoma Hospital.

20. Statistics on Pensions for the Blind, from the Fifteenth Biennial Report, Missouri Commission for the Blind, 1943-1944.

CONDITIONED CORNEAL VASCULARITY IN RIBOFLAVIN DEFICIENCY

Report of a Case

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IN 1940 Sydenstricker and his associates [1] published their observations on corneal vascularization in man, which was similar to that described previously by Bessey and Wolbach [2] in rats maintained on riboflavin-deficient diet. Since then a large number of papers on the subject have appeared, and the first enthusiastic response of confirmation soon made way to criticism and doubt; the latter trend, as happens frequently, shifted the general opinion far in the opposite direction, causing a number of workers to deny the existence of corneal vascularity as a result of ariboflavinosis in man. This negative attitude seems to have taken root to a certain extent in the collective mind of ophthalmologists.

Corneal vascularity caused by riboflavin deficiency is a clinical entity. It is probably true that it cannot be diagnosed by its morphologic aspect alone, although the appearance of regular, fine capillaries in the entire circumference of the cornea, which leave the limbic zone and pass centripetally into the clear cornea, is highly suggestive; if, in addition, three conditions are fulfilled—inadequate riboflavin intake, low riboflavin level of the blood or urine and response to treatment with riboflavin—there is no doubt as to the cause of the lesion.

The following case report is presented because any additional clinical observation on the relation of this lesion to riboflavin deficiency is worthy of attention if it establishes the validity of the concept first expressed by Bessey and Wolbach and by Sydenstricker and associates.

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Part of the expenses connected with this investigation was met by a grant from the Nutrition Clinic Fund.

From the Nutrition Clinic of the Department of Health of the City of New York, and the Special Eye Bank Clinic of the Manhattan Eye, Ear and Throat Hospital, New York.

1. Sydenstricker, V. P.; Sebrell, W. H.; Cleckley, H. M., and Kruse, H. D.: Ocular Manifestations of Ariboflavinosis: Progress Note, J. A. M. A. **114**:2437 (June 22) 1940.

2. Bessey, O. A., and Wolbach, S. B.: J. Exper. Med. **69**:1, 1939.

REPORT OF CASE

E. A., a Greek veteran aged 38, was sent to this country by his government to seek cure for blindness, which he had contracted during army service. It was hoped that a corneal transplant might benefit him, and he came to the Special Eye Bank Clinic (Manhattan Eye, Ear and Throat Hospital), where Dr. R. Townley Paton referred him to the Nutrition Clinic of the Department of Health of the City of New York for study.

His vision had always been adequate prior to a shell blast injury received to his face and eyes in the early stages of the Greek-Italian war (1940). At this time he was taken prisoner by the Italians, and he spent the next five years in Italian and German prison camps. During this time his eyesight deteriorated steadily, and when he was finally returned to his country he was blind for all practical purposes.

When he was first seen at the Nutrition Clinic, he was a thin, dejected-looking man, who was hardly able to find his way in unfamiliar surroundings. His vision

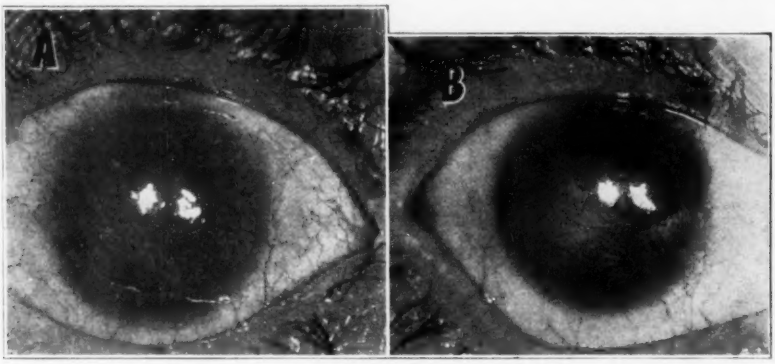

Fig. 1.—Eyes before riboflavin therapy was started. *A*, right eye. *B*, left eye. Note the irregularity of the normally circular light reflex on the cornea, indicating the degree of unevenness of the epithelium.

was reduced to counting fingers at 2 feet (60 cm.). Both eyes showed injected conjunctivas, and photophobia was present. Both corneas showed diffuse opacities over the entire surface, chiefly in the superficial layers and the epithelium, with numerous engorged blood vessels entering the cornea from every point of the periphery, traversing it and freely communicating with each other. On the posterior surface of each cornea and the anterior surface of the lens, fine and gross particles of iris pigment could be discerned (fig. 1 *A* and *B*). There was dyssebacia of the face, but no glossitis or cheilosis.

A reconstruction of his diet during the war years showed that he had been on a diet seriously deficient in all members of the vitamin B complex, as well as in other vitamins. Riboflavin must have been practically absent from his diet. During all these years he had formed a faulty dietary pattern, and even now, with all restrictions removed, he consumed a diet inadequate in riboflavin. Examination of the urine for riboflavin at the Nutrition Clinic showed 70 micrograms in a four hour fasting specimen of 340 cc., a value indicating a low riboflavin intake.

Treatment was instituted with administration of 15 mg. of riboflavin by mouth. After one week, regression of the hyperemia of the corneal vessels could be observed, and the cutaneous lesion on the face was clearing. By the end of the third week the vessels in the cornea were considerably less noticeable. Some of the smaller ones could not be seen at all with the slit lamp, and the larger ones were less engorged and showed a reduction in caliber. Vision had improved to counting of fingers at 6 feet (180 cm.). The patient had gained 3 pounds (1.3 Kg.) and felt much better generally.

At the end of seven weeks, with no additional therapy, the majority of the vessels in the cornea had become invisible. Here and there, blood corpuscles could be seen in collapsed capillaries. In other capillaries very sluggish circulation was still evident. The opacities had receded considerably, and the patient counted fingers at 10 feet, or 3 meters (fig. 2). (He was myopic, and the visual acuity could still be improved with glasses.)

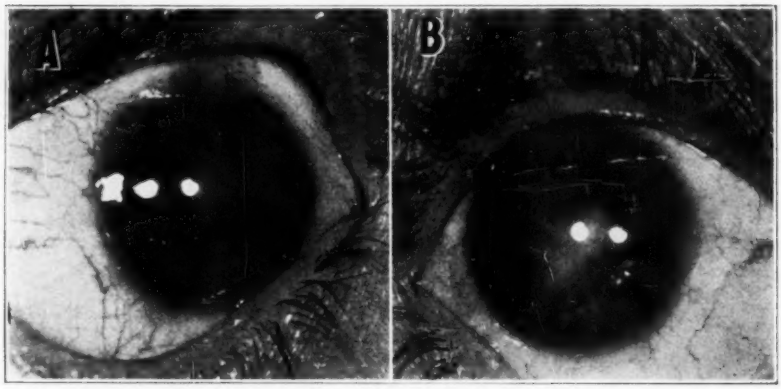

Fig. 2.—Eyes seven weeks later. *A*, right eye. *B*, left eye. Note that the light reflexes on the cornea are nearly circular, indicating that the epithelium is now almost normal.

There does not seem to be any reason to doubt that this case was one of true riboflavin deficiency. All the conditions are fulfilled: low riboflavin intake over a long period, low riboflavin level of the urine and prompt response to riboflavin therapy. Although a deficiency of all vitamins was probably present, only riboflavin was given as a therapeutic trial. It is hardly conceivable that pathologic changes of the degree described would recede spontaneously after having been present so many years. It can be concluded, then, that a long-standing deficiency of riboflavin in this patient's diet resulted in the specific lesions in his eyes, which were influenced most favorably by specific therapy.

This explanation, nevertheless, is not fully satisfactory. There must have been a very great number of people under nutritional handicaps similar to those of this patient during the war and the postwar years.

Yet, during the last few years, thousands of prisoners of war and inmates of concentration camps have been seen by a number of investigators, without any published reports indicating the presence of corneal vascularity in the degree seen in the present case. It appears, then, that the nutritional factor is not the sole explanation of the corneal vascularity in this case. An additional factor must have been present which, in combination with riboflavin deficiency, produced the clinical picture.

It has been shown by Bessey and Lowry [3] that the riboflavin concentration in the cornea of the rat must fall to less than 50 per cent of the normal before signs of corneal vascularity appear. Clinical investigations now under way seem to indicate that chronic riboflavin deficiency may produce corneal vascularization only if and when the cornea is exposed to a traumatic factor—be it accidental injury, surgical intervention, chronic mechanical or solar irritation or an allergic reaction. Landau and I [4] have argued the case for the last contingency in the instance of eczematous keratitis. The present case seems to support a position of major importance for trauma. During his army service the patient was subjected to bomb and shell blast on several occasions, and on one of these he received the full blast of an exploding shell in his face. The iris pigment scattered over the surfaces of the anterior chamber in both eyes was probably a result of this blunt injury. It seems justifiable to assume that the cornea was injured superficially and that the healing process was disturbed by the presence of a serious riboflavin deficiency.

Riboflavin is a prosthetic group of the yellow respiratory enzyme. Bessey and Wolbach [2] postulated that in its absence the disturbance of the respiratory processes in the avascular cornea is relieved by ingrowing vessels. Contrary to earlier opinions, the metabolism of the corneal epithelium is very active (Lowry and Bessey,[5] Robbie and associates [6]). An injured cornea requires more oxygen, consequently more respiratory enzyme, and therefore more riboflavin, than a healthy one. A degree of riboflavin deficiency which will remain subclinical under normal conditions will lead to corneal vascularization to relieve the respiratory deficit when pathologic conditions raise the corneal metabolism. It has been shown by Lowry and Bessey [5] that a prolonged deprivation of riboflavin leads to a fall in the riboflavin concentration in the cornea, causing a definite handicap to the healing of experimental lesions.

The corneal condition in the case presented here had remained static for many months. The patient had received the usual local treatment

3. Bessey, O. A., and Lowry, O. H.: J. Biol. Chem. **155**:635, 1944.

4. Stern, H. J., and Landau, J.: Am. J. Ophth. **31**:1619 (Dec.) 1948.

5. Lowry, O. H., and Bessey, O. A.: J. Nutrition **30**:285, 1945.

6. Robbie, W. A.; Leinfelder, P. J., and Duane, T. D.: Cyanide Inhibition of Corneal Respiration, Am. J. Ophth. **30**:1381 (Nov.) 1947.

and had failed to show any response. The improvement under riboflavin therapy was too dramatic to be explained by anything but the contention offered here. It can safely be assumed that in this case a chronic deficiency of riboflavin had been "conditioned" (Jolliffe[7]) by superficial injuries to the cornea, the nutritional factor complicating their healing and causing the extensive opacities and vascularity which rendered him nearly blind. Specific therapy with the missing vitamin relieved this condition to such a degree that the patient acquired useful vision within a few weeks, thus obviating the necessity of corneal transplantation.

3 Hopper Street.

7. Jolliffe, N.: Conditioned Malnutrition, J. A. M. A. **122**:299 (May 29) 1943.

PERSONALITY PATTERNS IN OCULAR DISCOMFORT

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HONOLULU, T. H.

THE MOST frequent reason that patients seek the services of an ophthalmologist is their inability to use their eyes with comfort. As a rule, the patient with visual impairment does not come into a physician's office early but tends to procrastinate. The causes of ocular discomfort are many, but no attempt will be made to give a differential diagnosis of ocular discomfort here. Rather, I shall analyze observations on a group of patients with ocular discomfort other than that due to refractive errors, improperly made glasses or poorly adjusted glasses, as discussed by Veasey.[1] These patients form a distinct group whose complaints are real and whose symptoms cannot be relieved by merely treating the patient as a rigid optical apparatus, without regard for his personality, of which the ocular component is only a small part. If the physician but understands the personality patterns of these patients and if, after finding nothing abnormal on refraction and examination of the eyes, he takes the time to explain to them the possible root of their trouble and to give them the advice and reassurance that is necessary for the relief of their symptoms, he will have served them both as a physician and as an ophthalmologist.

In the study of ocular discomfort, it is of the utmost importance that a good history be obtained. The patient can usually give a rather definite time of onset of his symptoms. This is important, as the circumstances leading up to the evolution of his symptoms will usually give a clue to his reactions to various life situations, which must be understood before his complaints can be evaluated properly. At present, the ocular findings are usually pointed out after the symptoms have developed, but there is no way of knowing whether or not the condition was the same before the symptoms occurred. If it is accepted that a discomfort, an ache and a pain are various degrees of response to a stimulus, whether the stimulus is internal or external, psychogenic or organic, it is evident that the difference between the degrees of pain experienced by the same person depends on the degree of stimulation. However, the same degree of stimulation will not elicit the same degree of response

1. Veasey, C. A.: The Dissatisfied Refraction Patient, Am. J. Ophth. **30**:1286-1293 (Oct.) 1947.

in different persons. It is not the stimulus itself, therefore, but the impact of the stimulus on a particular kind of person, that leads to symptoms of varying degrees.

ANALYSIS

Period of Onset.—Certain periods or situations in life will precipitate symptoms in persons of a particular type. Such situations are found between adolescence and middle age, the period of life in which the trial and stress of living show up the weak spots in a person's makeup. Symptoms of discomfort are rarely found in children because their emotive and mental attributes are not developed. Among such situations of stress are initiation into a job, a love affair, disappointment in vocational or financial affairs, pressure in establishing a place in the economic and social world, a death in the family, marriage, pregnancy, the menopause and incidents of adjustment in later life.

Personality Characteristics of Groups.—Such patients tend to be of a definite physical type. Women predominate over men, the ratio being about 8:2. In general, these patients are slenderly built. They dress neatly and well despite their actual economic station. Their habits and actions are orderly and well planned. This orderliness in their manner of dress and habits extends to their home and place of work, so that if anything is out of place they feel uneasy until order has been restored. They are endowed with a great deal of energy and "push" and appear tireless in their pursuit of the goal that "everything be just so." This inflexibility reflects itself in their actions and thinking. Such persons cannot delegate anything to be done by someone else, for they feel that no one can do it as well as they. This unyielding approach to life makes readjustment and compromise difficult, so that, rather than adapt themselves to a difficult situation in life, they resist and balk at the expense of their emotional system.

Ocular Complaints.—The ocular complaints of such patients are definite, although they vary in degree with the individual. He exhibits a characteristic quality of ocular sensitiveness or ocular consciousness which is above the average. There is a history of inability to read or sew, even for short periods, such activity usually being followed by a vague ache in the eyeball or along the supraorbital ridge, with later extension as the sensation of a tight, gripping band about the head. A great deal of exactness and detail is used in outlining the particular site of the ache and its ramifications. In such a description, one gets the impression that the vague ache has at times become almost unbearable and yet is stoically endured. Photosensitivity is rather characteristic, and the patient professes to have relief from the use of tinted or dark glasses. Even the glare of an ordinary light bulb causes such

a patient to change his sitting position in relation to the light, whereas other persons may not be disturbed by the same amount of light. The sensitiveness to light is a reflection of ciliary (cortical?) sensitivity, and the aching about the eyeball is a manifestation of ciliary spasm. Refraction with cycloplegia usually gives the patient relief from his symptoms for the time being. Spasm of the sphincters of the body is a common complaint of nervous, unduly irritable women, as has been pointed out by Alvares [2]; but why the sphincter of the eyes is a source of discomfort in one patient, and the sphincter of the pharynx, the pylorus or the anus in another, is difficult to explain. These sphincteral sites of physical disturbances are merely targets of a tensional state the expression of which in a particular sphincter depends on the emotional experiences and stability of the particular patient. That is to say, one's past experiences and associations have a definite influence on the manner in which one thinks and acts and feels (reacts).

Experimental Work.—Of extreme interest is the work of Cyriax,[3] who injected 0.1 cc. of a 4 per cent sodium chloride solution into the occipital insertions of the muscles of the neck, with the development of pain which ran forward like a band encircling the head and reached its maximum intensity in the temple and the supraorbital region. When the injection was made about 2 inches (5 cm.) below the occipital insertion, the pain was referred from the back of the head to the vertex. When the injection was made in the sternocleidomastoid muscle, the pain was referred to the temple. When the injection was made in the epicranial aponeurosis, the pain was referred to the eye, behind the eye and to the eyelids. Of particular importance is the fact that with each of these types of referred pain the patient interpreted the pain as being inside the head and that it bore no relation to its actual, superficial cause.

According to Wolff,[4] the most commonly encountered headaches are vascular, and these include migraine and tension headaches, which arise from sustained contraction of the muscles of the head and neck. Pain in the head, of whatever cause, may induce secondary contraction of the muscles of the head and neck, which when maintained becomes a source of pain in itself. Thus, a vicious cycle may be initiated, which, if unchecked, may cause a fixation of the condition, with resulting irreversible organic changes.

Systemic Complaints.—It is not uncommon for these patients to have many systemic complaints, in addition to those related to the head and neck. There is often a complaint of generalized muscular fatigue without

2. Alvares, W. C.: Psychosomatic Medicine That Every Physician Should Know, J. A. M. A. **135**:704-708 (Nov. 15) 1947.

3. Cyriax, J.: Rheumatic Headache, Brit. M. J. **2**:1367-1368 (Dec. 31) 1938.

4. Wolff, H. G.: Headache and Other Head Pain, New York, Oxford University Press, 1948.

any tangible cause. Many such patients give the history of going to bed early to get rested, only to get up the next morning feeling just as tired as before. It is of interest to note the observation of Allan,[5] in a study of 300 patients with complaints of weakness and fatigue, that physical causes were found in only 20 per cent, whereas in 80 per cent the condition was attributable to a nervous condition. The patients are generally poor eaters and give a history of trying to gain weight but of being unable to do so. They all give a history of insomnia and are rather light sleepers. They tend to dream a great deal, and many plan their day's work in their insomnic state, so that they know just what they are to do the next day. This is in keeping with their determined perfectionistic, yet cautious, attitude toward life and their constant preoccupation with acquiring achievement and success. Although the personalities of these patients seem to fit a definite pattern, not all patients with the aforementioned characteristics complain of ocular discomfort. A person becomes what he is because of his individual accumulation of experiences and associations. Although many of these experiences are common to most people, it is the manner in which the individual person reacts to his emotional experiences that causes him to be what he is.

Ocular Findings.—These patients usually have a low refractive error. On refraction with cycloplegia, they will be found to be hypermetropic, and when a postcycloplegic refraction is done they prefer a minus lens. Their visual acuity is 20/20 without glasses, yet they prefer the sharp, dark outline that the minus lenses afford them. However, these lenses give only a temporary subjective relief, after which the patient feels better without them. The relation of abduction to adduction is not the 1 : 2 or 1 : 3 ratio which is usually given in textbooks. Analysis of the complaints of 100 patients in relation to the abduction-adduction ratio revealed that their prism vergences for near and far had no relation to their complaints. In fact, some who should have been uncomfortable according to their prism vergence ratio had no complaints at all. It is evident, therefore, that it is not the duction power per se, but, rather, the patient's threshold of sensitiveness, that is important for ocular comfort. If this is low and the strain is too great, the body rebels and symptoms of ocular or juxtaocular discomfort result in susceptible persons.

Orthoptic Training.—The purpose of orthoptic training of adults is to produce comfortable binocular vision. Healy [6] discussed "symptom-free" and "symptom-producing" heterophorias and emphasized that the

5. Allan, F. N.: The Clinical Management of Weakness and Fatigue, J. A. M. A. **127**:957-960 (April 14) 1945.

6. Healy, E.: Treatment of Phorias in Adults, Am. J. Ophth. **31**:703-708 (June) 1948.

patient who manifests a "symptom-free" heterophoria, regardless of the degree, is best left untreated. For best results, the process of fusional exercises necessitates a willing and cooperative patient. His improvement is related directly to his interest in the exercises. He thus replaces an uncomfortable visual reflex by a comfortable one. Bahn [7] recognized patients of this type and outlined a daily routine which aims at regimenting the patient's daily routine so that he has little time to think about his symptoms. In this therapy, the role of the physician and the orthoptic technician as a target of the psychiatric process of transference plays an important part in the ultimate success of relieving symptoms of discomfort.

COMMENT

Many of these patients have made the "rounds" of the ophthalmologists in the community. If the patient has been wearing glasses, a reduction or an increase in the power or a change in the axis of the cylinder is usually made, with only temporary relief in trial frame tests. In 1 case, three oculists changed the axis of a + 25 cylinder 5 to 15 degrees, with only temporary relief of symptoms. The urge to sell glasses is so great that it often prejudices the ophthalmologist in prescribing glasses when he knows they will do little good. Derby [8] stated that "there is entirely too much changing of lenses a fraction of a diopter or a few degrees of axis among us [ophthalmologists] and naturally so because it is the path of least resistance." In a review of 1,000 consecutive single vision prescriptions of a moderate-sized optical house, it was found that 200 were in the group of — 25 or + 25 cylinders or less. Of these 200 prescriptions, a not too small portion consisted of + or — 12 spheres or cylinders. Thus, in this community at least, approximately 20 per cent of the prescribed single vision lenses are worn by patients whose benefit cannot be attributed to the optical effect of the lenses alone.

The majority of these patients will be found to have been fairly comfortable up to a certain point in their lives, when their train of symptoms emerged. At that time, if an ocular examination was conducted, a small refractive error may or may not have been found; a muscular imbalance was usually discovered with a disturbance in the accommodation-convergence relation. If the same patient were examined before his symptoms developed or after his symptoms subsided, a similar small refractive error would be found and the prism vergences would not be changed too greatly (unless an educational process has been entered on through the medium of orthoptics). The ocular findings per se will not result in symptoms of ocular or juxtaocular discomfort, but the response to a situation in life or to a series of accumulative experiences

7. Bahn, C. A.: The Psychoneurotic Factor in Ophthalmic Practice, Am. J. Ophth. **26**:369-378 (April) 1943.

8. Derby, G. S.: Ocular Neurosis, J. A. M. A. **95**:913-917 (Sept. 27) 1930.

in life may result in symptoms of ocular discomfort in a susceptible person. If the emotional development has been normal, the symptoms will subside without much ado, but if it has been retarded symptoms will persist. The cure lies in the physician's understanding the emotional background of the patient and in the patient's readjusting his thinking and mode of living.

An illustrative case is that of a patient of the bifocal age who had seventeen pairs of glasses prescribed in three years. He was subject to frontal headaches, which prevented him from working at his desk for any length of time. He was seen by seven or eight ophthalmologists, several nose and throat men and several general practitioners. Each told him he could not find anything wrong. The otolaryngologist removed his tonsils. Each ophthalmologist changed his prescription slightly once or twice. From the patient's history, it was learned that when he took a three month vacation he had no headache and enjoyed his reading. His glasses were correct for pupillary distance in far and near vision and were of equal power. It was learned that he was insecure at his job, and it appeared that his headaches were an escape which he was able to use whenever responsibilities were too great. He was told that there was nothing wrong with his eyes, for if there were he should, by all rules, be just as uncomfortable with them on his vacation as he was at his job. He volunteered the information that when he worked in his garden he was relieved of his headaches for several days. He was encouraged to get out-of-doors for more of his activities and obtained some relief from his symptoms; but, because of the prolonged fixation of his symptoms, it was difficult for him to modify his manner of thinking and feeling. Although he did get relief from his headaches for various periods, he had used the protective shade of his headache for so long that he could not give it up entirely.

If one treats the eyes merely as optical units, correcting whatever minor defects may be found, one cannot hope to obtain a cure of the symptoms when the eyes are merely the portals through which a deranged emotional system gives vent to its inability to live within its means. It cannot be denied that the mere wearing of weak lenses will often be sufficient to give a person temporary relief from his symptoms. There is no way to determine whether the optical correction of the small refractive error was sufficient to raise the threshold of irritability and give relief or whether the psychologic effect of the weak lenses was enough to counteract (cortically) the results of a minor emotional upset. One might say: "If the lenses give relief, who cares in what manner they do this; but if they do not, then one must seek the cause elsewhere." Of course, when glasses are given the patient with a verbal psychologic vehicle that they will help, the element of suggestion, together with the factor of transference, comes into play, and the lenses merely become

the symbol of a minor psychiatric ritual. In this case, and the patient is temporarily relieved, one might say: "Why bother?" However, among these patients are persons whose emotional stability is poor; and if the physician does not recognize the personality patterns, he may allow the patients to continue into a neurotic morass, from which, at a later period, they may need a major psychiatric "over-haul" to make them useful to themselves, to their families and to their community.

MECHANISM

The evolution of ocular discomfort may be explained in the following manner: When the stress of living begins to affect a susceptible person, something occurs in that person which causes him to react with more than normal lability to the ordinary situations in life. This sensitivity is a manifestation of a lowered cerebral threshold to a trying situation. The normal person soon learns to adjust himself to the situation, and there is no conflict. However, in the susceptible person the conflict causes an undue amount of concern, which acts through the hypothalamus to produce symptoms. Ill sustained accommodation, transient weakness of accommodation and excessive accommodation may occur, as do other disturbances of the autonomic system, at times of worry or emotional stress.[9] There is reflex distention of the cerebral arteries, with radiation of pain in the region of distribution of the ophthalmic branch of the fifth nerve. A reflex spasm of the ciliary body may be produced, with resulting ciliary pain. The patient, therefore, complains of blurring of print, so that it takes him a moment to get things into focus, by blinking or by momentary forceful concentration. He complains of photophobia without any evidence of organic change within the eye. He may also complain of seeing double when he is tired.

TREATMENT

Treatment of such a patient should consist, first, of obtaining a good history of the onset and course of his present complaints. The patient should be permitted to tell his story in his own, unchronologic way, for from this account one can often learn whether the condition is functional or organic. A complete examination of the eyes, including refraction with cycloplegia, should be made. In his study, the physician must have an interest in and understanding of human beings and their problems, as well as knowledge and understanding of diseases in general. In many cases one may be on the receiving end of an emotional catharsis, and merely the lending of a sympathetic ear to the patient's discharge of emotional tension may be all that is needed. In other cases the relation of the emotion to the symptoms may be explained to the patient, or, better

9. Cogan, D. G.: Accommodation and the Autonomic Nervous System, Arch. Ophth. **18**:739-766 (Nov.) 1937.

still, the patient may be permitted to realize this himself, so that at the postcycloplegic examination this realization will be complete. In the more resistant cases the patient's confidence is not won, and it may be necessary to have the element of time enter into the picture, so that the factor of transference may take place. The use of placebos, such as vitamin preparations and small doses of phenobarbital, may permit one to gain this element of time. Of course, the danger in the use of placebos may be a fixation in the patient's mind that something is actually wrong —otherwise the physician would not give him medicine. The real danger in treatment in these cases is to overlook a truly ocular cause that is amenable to ophthalmologic therapy and to call such a case one of ocular neurosis. On the other hand, it is just as much an error to continue to treat the patient from the standpoint of the eyes when the service of a trained psychiatrist is indicated.

Davis [10] stated the belief that the ophthalmologist should treat these patients rather than refer them elsewhere (unless for diagnostic work-up), for, in his opinion, the ophthalmologist is in an ideal position to care for the patient because of the nature of the complaints. As long as ophthalmology consists in caring for patients from a medical, as well as from an ophthalmologic standpoint, many of these patients can be turned early in their neurotic course.

It appears, therefore, that what really must be treated in these patients is their emotional sensitivity and the ideas which are behind their sensitivity. The patient should be told, after a thorough examination, that his eyes are normal. It then becomes a matter of having him understand the manner of his thinking and feeling toward conditions and people with whom he is associated. In other words, a reeducational program is started, and the patient is taught to develop a new mode of thinking and of reacting to various life situations. When the patient learns to adapt himself to his problem, there is no conflict and, as a result, no symptoms.

CONCLUSIONS

Persons with ocular discomfort of nonorganic nature have personality characteristics of a definite pattern. Relief of their symptoms consists in helping them to understand their emotional background and directing their energies into less conflicting channels.

1221 Victoria Street (34).

10. Davis, W. T.: Astenopia and Headaches Not of Ocular Origin, New Orleans M. & S. J. **88**:159-167 (Sept.) 1935.

Case Reports

TERATOMA OF ORBIT

CAPTAIN F. HARBERT (MC), U.S.N.

CONGENITAL tumors are classified embryologically according to the number of germ layers from which the tumor is derived. Thus, osteoma and angioma are derived from a single germ layer. Dermoids are characterized by tissue derived from two germ layers, viz., ectoderm and mesoderm. These tumors are characterized by the presence of squamous epithelium and of its derivatives, such as hair, nails, teeth and sudoriferous and sebaceous glands. The dermis, derived from underlying mesenchyme, may become differentiated to form cartilage, bone, fat, muscle or other specialized tissue. Dermoids may occur as cysts or solid tumors. In the cyst, the dermis is on the outside and the epithelium lines a cavity, usually filled with inspissated, oily secretion and hair. In the commoner, solid type, the epithelium is exposed to the surface of the body, and a common site is astride the corneal margin. Solid dermoids are commoner than the cystic variety about the orbit.[1]

The commonest locations of dermoid and teratoma are the ovaries, testes and sacral regions, but they have been reported in nearly every part of the body. An analysis of dermoid cysts seen at the Mayo Clinic from 1910 to 1935 showed that of 1,495, 45 per cent occurred in the postanal region, 42 per cent in the genitalia, 7 per cent in the head and neck and 6 per cent elsewhere.[2] Of the dermoids of the head and neck, one half were in the orbital region, and of these 60 per cent occurred in the outer third of the eyebrow. Half of these were noted at birth. Only 10 per cent of the dermoids of the orbital region (6 in twenty-five years) were within the orbit, usually in the upper outer quadrant of the right orbit.

True teratomas must contain tissue derived from all three germ layers. Such tumors are exceedingly rare in the orbit and are usually

From the United States Naval Hospital, Philadelphia.

Read at a meeting of the College of Physicians of Philadelphia, Section on Ophthalmology, Dec. 18. 1947.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth are those of the author and are not to be construed as reflecting the policies of the Navy Department.

1. Rosen, E.: Bilateral Teratoid Tumor of the Limbus, Arch. Ophth. **32**: 120-122 (Aug.) 1944. Sherman, A. R.: Teratoid Tumor of the Conjunctiva and Other Development Anomalies with Naevus Verrucosa of the Scalp, ibid. **29**: 441-446 (March) 1943. Badier, G.: Solid Dermoid of the Lid Border, Bull. Ophth. Soc. Egypt **34**:65-67, 1941.

2. New, G. B., and Erich, J. B.: Dermoid Cyst of Head and Neck, Surg., Gynec. & Obst. **65**:48-55, 1937.

Fig. 1.—Appearance of child on day after birth (Dec. 11, 1946).

Fig. 2.—View in February 1949 with prosthesis, showing ptosis, which will be corrected later.

malignant.[3] Identification of tissue derived from the endoderm is sometimes difficult, and some pathologists rely on the complexity and variety of tissue in making a diagnosis of teratoma. The finding of tissue con-

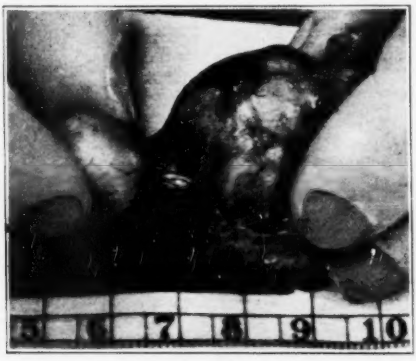


Fig. 3.—Excised specimen, showing optic nerve entering tumor.

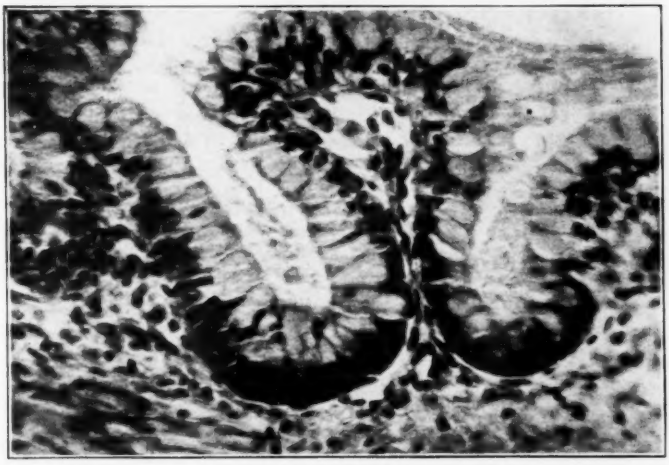


Fig. 4.—Mucous membrane with goblet cells in characteristic arrangement of the intestine.

3. (*a*) Samuels, B.: Dermoid Cysts of Orbit, Tr. Am. Ophth. Soc. **34:** 226-230, 1936. (*b*) Mann, I.; Developmental Anomalies of the Eyes, London, Cambridge University Press, 1937, pp. 411-412. (*c*) Burnier, P., and Salles, M.: Teratoma of Orbit, Arq. Inst. Penido Burnier **7:**114-128, 1945.

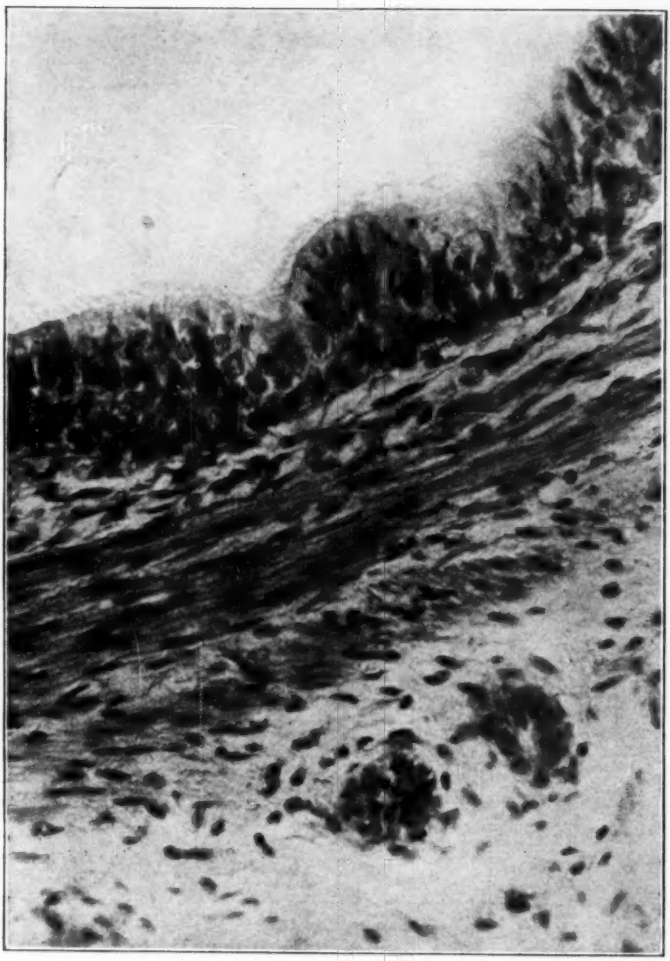


Fig. 5.—Ciliated columnar epithelium.

sisting of cavities lined with pure mucous epithelium with an arrangement characteristic of gut is considered diagnostic of endodermal origin. The dermoid variety is often referred to in the literature as teratoma, teratoid tumor, mixed tumor or epibulbar tumor.

A perusual of the literature for the past ten years revealed only 1 case of teratoma of the orbit.[3c] This case was very similar to the case reported here in that the tumor was present at birth, an intact eye surmounting the tumor. This eye was permitted to ulcerate, operation being deferred for two months. A cleavage line was easily found, and exenteration of the orbit resulted in an apparent cure at the time of reporting, two years later. The clinical diagnosis was confirmed

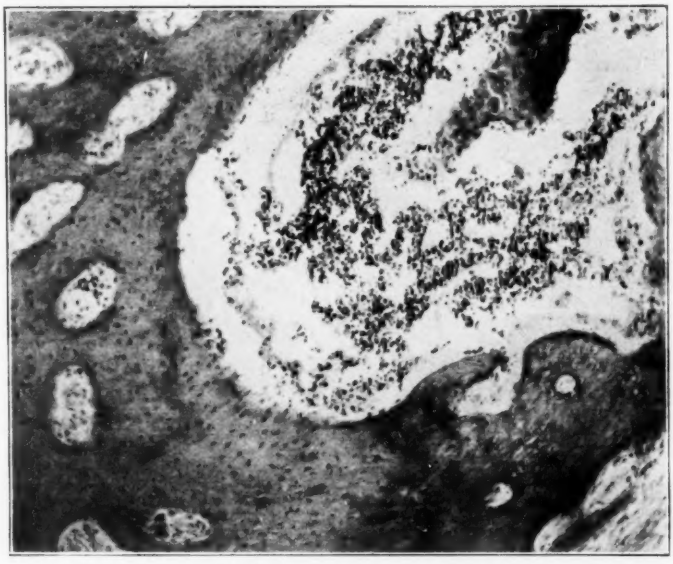


Fig. 6.—Young bone with central marrow cavity and bone marrow.

pathologically. A review of the literature by Burnier and Salles indicated that 17 cases of true orbital teratoma had previously been reported.

REPORT OF A CASE

Baby M. was born Dec. 11, 1946 with a very large mass in the left orbit, causing pronounced proptosis. At birth the conjunctiva and cornea were normal, but within twenty-four hours the conjunctiva became increasingly chemotic and the cornea showed beginning cloudiness and infiltration. This process continued in spite of moist chamber dressings during the following two days, before permission for operation was obtained. The cornea was well formed and measured 9 mm. in diameter. The globe could be palpated through the mass and seemed to be

flattened anteroposteriorly. Behind the globe a solid tumor filling the entire orbit could be palpated. The outline of the mass was smooth except inferiorly, where several nodules were felt. Transillumination of the mass revealed the same consistency as that of the cheek. The globe was transilluminated clearly. A

Fig. 7.—Atypical structure lined with ciliated columnar epithelium.

needle passed into the mass for diagnostic aspiration failed to reveal fluid. The eye was not fixed, but motion was restricted to random, irregular, very slow oscillations.

The iris of the right eye was normally blue, but that of the proptosed eye was dark brown. The pupil was miotic but dilated well with atropine. Examination with the slit lamp showed persistence of a well marked marginal vessel in

the pupil. Roentgenograms of the orbits showed distinct enlargement of the left orbit, with intact bony walls.

Physical examination revealed no other developmental defects, and the right eye was normal. A clinical diagnosis of microphthalmos with cysts was made, and exenteration of the orbit was advised at once to prevent deep infection of the

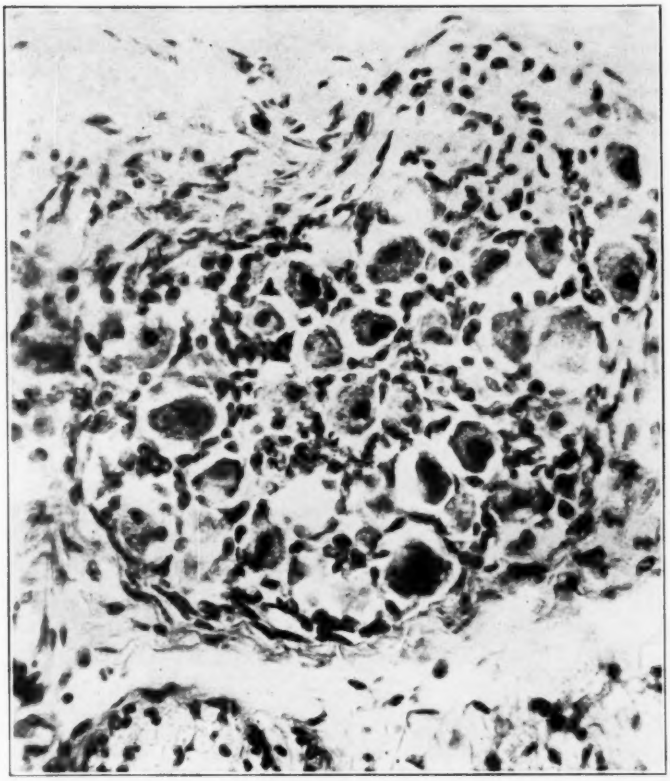


Fig. 8.—Large ganglion cells.

eye and orbit, which was considered inevitable because of exposure and edema.[4] Permission for operation was obtained on the third day.

Operation was performed with infiltration anesthesia, with no objection from the patient except to the injections. Two per cent procaine hydrochloride with epinephrine hydrochloride (1:1,000) was injected into the lids and along the

4. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, pp. 1268-1274.

orbital walls to the apex in minimal amounts and the conjunctiva was anesthetized by instillations of tetracaine hydrochloride U. S. P. The conjunctiva was first separated at the limbus on the temporal side, and the globe and outer aspect of the mass were exposed to ascertain the relation of the mass to the eyeball and to determine whether the mass was resectable without sacrificing the eye. It soon became apparent that the optic nerve passed through, and seemed an integral part of, the mass and that the extraocular muscles and Tenon's capsule were so attenuated that they were not recognizable. An incision into the exposed mass showed that it was composed of solid tissue with multiple cysts containing clear fluid. A line of cleavage between the mass and the periorbita was readily obtained, and the mass was easily separated.

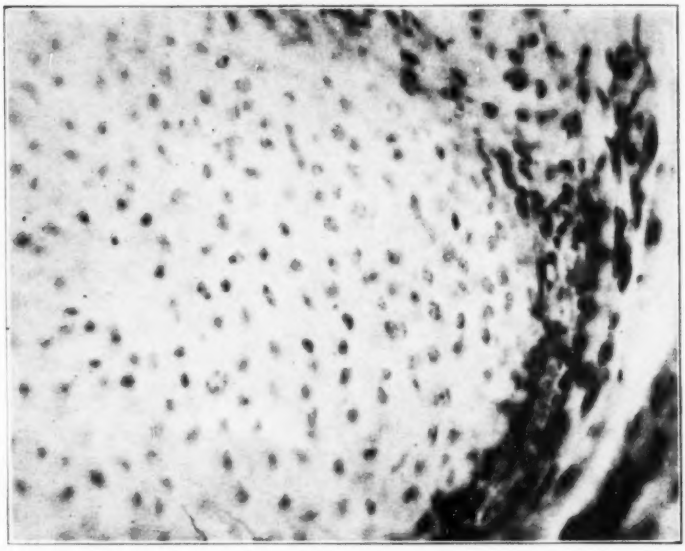


Fig. 9.—Young cartilage.

The entire orbit was filled with tumor, the mass extending to the orbital fissures and the optic foramen. When the eye and the mass were removed, a plastic implant was placed in the apex of the orbit and the conjunctiva was closed over it. A conformer was inserted in the conjunctival sac. When healing was completed and contraction of the cul-de-sac had been established, the conformer was replaced with an acrylic prosthesis made from a casting of the cavity. This has been worn continuously since (fig. 2).

Measurement of the excised specimen showed the globe to be 18 by 19 mm. at the equator and 15 mm. in the anteroposterior axis. The retrobulbar mass was roughly 5 by 4 cm. and contained multiple cysts on the surface (fig. 3).

Convalescence was uneventful, and the child is developing normally, with no evidence of recurrence to date.

Fig. 10.—Squamous epithelium with hair follicles and sebaceous glands.

Pathologic Study.—Microscopic sections of the excised specimen were examined by Dr. J. S. Friedenwald at the Wilmer Institute. His diagnosis was teratoma of the orbit, microphthalmos, exposure keratitis and hypopyon ulcer of the cornea.

The globe was rather small. The cornea was infiltrated and scarred. The anterior chamber was filled with polymorphonuclear leukocytes. Many such cells were seen in the iris stroma, and there was an abscess in the ciliary body. There were many retinal and subretinal hemorrhages and a few tiny choroidal hemorrhages. The optic nerve showed partial atrophy.

The tumor was a large cystic mass containing fat, bone, cartilage and many cysts, which were lined with epithelium of varying forms. The epithelial forms included squamous epithelium with many hair follicles and sebaceous and sudoriferous glands, ciliated columnar and cuboidal epithelium and mucous membrane with a papillary structure and arrangement characteristic of intestine. There were also small scattered glands of the racemose type, resembling salivary or lacrimal glands.

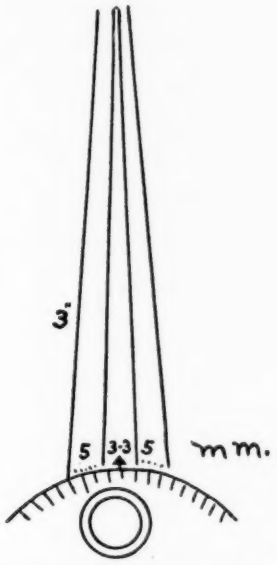
The matrix of the tumor was young connective tissue. Embedded in this matrix were lymphoid follicles with germinal centers, bone marrow and nerve tissue, including large ganglion cells.

Clinical Notes

SUSPENSION OF UPPER LID DURING INTRAOCULAR OPERATIONS

PAUL C. CRAIG, M.D.
READING, PA.

IT HAS been found convenient and satisfactory to dispense with speculum and retractors for intraocular operations, particularly during the critical stages. In their stead an upper lid suture is used, which is described here.



Placement of suture in the upper lid.

UPPER LID SUTURE

Suture Material.—The suture is twisted 0000 black silk with atraumatic needle, 18 inches (45.7 cm.) long.

Placing of Suture.—The needle is introduced through the thickness of the skin of the upper lid 8 mm. to one side of the center of the lid margin, immediately above and as close to the cilia as possible. It is passed toward the midline and emerges 5 mm. from the point of entrance immediately above and as close to the cilia as possible. It is pulled through, leaving an end about 3 inches (7.5 cm.) long. It is now reintro-

From the Department of Ophthalmology, St. Joseph's Hospital.

duced 6 mm. from the point of exit, again immediately above and as close to the cilia as possible. It emerges 5 mm. from the point of entrance. A loop is formed between the two stitches, and this loop is made as long as the tail end of the suture. The needle end of the suture is cut to correspond to the length of the loop and the tail end.

Use of Suture.—Throughout the operation an assistant holds the loop and both ends of the suture between thumb and forefinger, giving a four point suspension of the lid. The assistant has an opportunity to lift, or rather to "carry," the lid, or he can relax it completely, as the progress of surgical procedure may indicate.

COMMENT

The department of ophthalmology of St. Joseph's Hospital at present uses thorough block akinesia and anesthesia, as well as the Atkinson retrobulbar injection for the lowering of intraocular pressure.

The next step in any intraocular procedure is the placement of the lid suture. A speculum is used for dissection of the conjunctival flap and for the corneoscleral suture, only if desired. At the end of the operation the lid suture is removed provided the lid margins can be approximated. If, however, the lid fissure remains open, the loop of the lid suture is pulled out and the two ends are fastened to the skin of the cheek with Scotch tape. The ends of the suture are now about 6 inches (30 cm.) long and are doubly reversed over the Scotch tape for better anchorage.

It may be of economic interest to know that the cut end of the lid suture with needle is utilized as a hammock suture for the superior rectus muscle. It is approximately 6 inches long and lends itself well to this purpose.

Experience has shown that "carrying" the upper lid appears to reduce the incidence of gaping of the incision. If vitreous should present itself, it seems to withdraw more readily on appropriate manipulation of the upper lid.

SUMMARY

An upper lid suture is described which may make intraocular procedures somewhat safer.

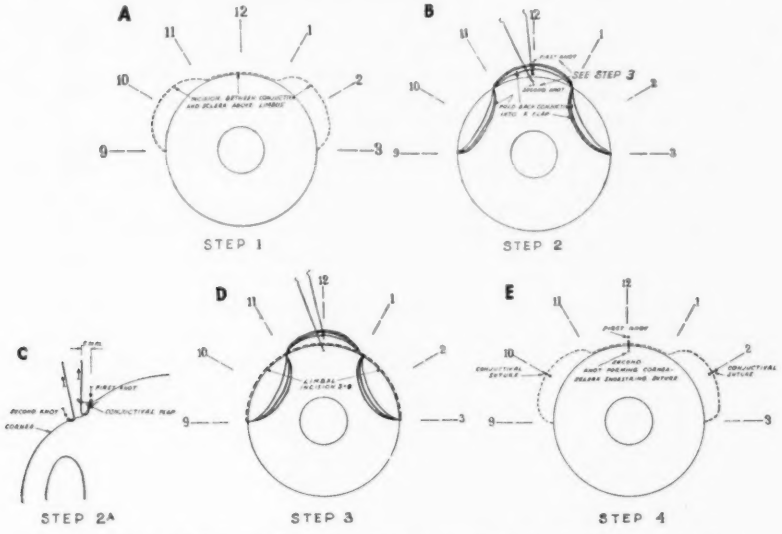
St. Joseph's Hospital.

A NEW SHOESTRING CORNEOSCLERAL SUTURE

GERALD D. SPERO, M.D.
DETROIT

I should like to recommend the following corneoscleral suture with modified conjunctival flaps.

1. A conjunctival incision is made along the limbus from 11 to 1 o'clock (figure, *A*). This part of the conjunctiva is then undermined



Steps in placement of a new shoestring corneoscleral suture: *A*, step 1; *B*, step 2; *C*, step 3; *D*, step 4; *E*, step 5.

From 1 to 3 o'clock a conjunctival flap 3 mm. wide is prepared. A similar one is made from 11 to 9 o'clock (figure, *B*).

2. A single-armed 000000 silk suture is knotted double. The needle is then introduced into the conjunctiva above 12 o'clock, about 5 mm. from the limbus, from without in. A vertical bite is then taken in the episclera 2 mm. above the limbus, the needle emerging as close as possible to the limbus. The needle is then reintroduced through the conjunctiva 2 mm. above the free border and brought out. This needle is then cut off. The suture is now anchored above in the episclera and outside the conjunctiva.

3. A second needle, similarly knotted, is introduced vertically in the cornea 2 mm. below the limbus at 12 o'clock and brought out as close to the limbus as possible. The needle is cut off and the thread pulled taut. There are now two threads, one below, anchored by a knot in the cornea, and the other above, in the episclera (figure, *C*).

4. After the sutures are ready, an incision is made, preferably with a keratome, along the limbus and enlarged with scissors (figure *D*).

5. When the lens is extracted, the central sutures are tied with a double loop. This prevents slipping of the suture. Two corneoscleral sutures, instead of one, can be used. After the iris is replaced, the conjunctival sutures are put in and tied (figure, *E*).

This suture has the following advantages:

1. The shoestring suture is easy to introduce.

2. The double knot does not cause any irritation to the cornea.

3. Introduction of sutures before section is much simpler than after.

4. There is practically no danger of cutting the sutures, for they are already cut. There are no loops in the way.

5. The closure is more rapid, and therefore complications, when they occur, can be handled with greater ease.

6. The lower suture is anchored into the corneal flap. By pulling on it slightly, the surgeon can get an excellent view of the lens during its extraction.

7. The absence of the conjunctival flap in the center permits greater visibility when the cataract incision is made. Enough conjunctiva remains, and conjunctival sutures can easily be introduced on either side of 12 o'clock.

Miss Connie Davis and Mr. Arnold assisted in preparation of the sketches for this article.

2311 David Broderick Tower (26).

Ophthalmologic Reviews

NEUROMYELITIS OPTICA (DEVIC'S DISEASE)

Presentation of Five Cases, with Pathologic Study, and Review of Literature

FREDERICK C. STANSBURY, M.D.
SYRACUSE, N. Y.

(Concluded from Page 335)

PATHOLOGIC FEATURES

The optic nerves received special attention from the early investigators of neuromyelitis optica. These writers stated that the pathologic condition of the spinal cord was an ordinary acute myelitis and that the involvement of the optic nerves represented an extraordinary pathologic phenomenon. The loss of myelin sheaths in the optic nerves was first recorded by Achard and Guinon,[6] who described almost complete disappearance of myelin in the optic nerves of their patient. Elschnig [11j] verified their observations in his case and described intraocular lesions; he noted extreme thinning of the nerve fiber layer of the retina, with diminution of the ganglion cells. Dalen [11q] reported the same alterations in the retinas of another patient with this disease. Dreschfeld [11l] wrote an excellent pathologic report of a case, in which he described perivascular infiltration and irregularly distributed patches of demyelination throughout the lesions. The centers of the optic nerves in Dreschfeld's case were completely destroyed; he observed sclerosis of the periphery of the nerves, with conversion of this portion into a mass of connective tissue. In 2 cases in which autopsy was performed Holden [60] noted areas of softening in the spinal cord, with rarefaction of tissue, glial overgrowth in places and extensive cellular infiltration about the blood vessels.

In the case published by Devic,[7] the lesions were observed in the periphery of the optic nerves; the myelin sheaths in these foci had not completely disappeared, although the remaining myelin was fragmented and discontinuous for considerable distances. Devic described perivascular spaces crowded with small round cells and infiltration of the interstitial tissue of the nerves with these same cells. He also reported the destruction of myelin sheaths and disintegration of anterior horn cells in the spinal cord. Katz [11n] found that the optic nerves were grossly much reduced in size and that microscopically the centers of the nerves were completely degenerated. In a monograph containing detailed, minute observations on the pathologic changes in 4 cases, Bielschowsky [62] described destruction of the optic nerves as far back

as the chiasm in 1 case and degeneration through the whole optic pathway in another. There were scattered areas of softening, with infiltration of round cells about the blood cells running into these foci. In the severe lesions Bielschowsky noted destruction of nerve fibers, increased interstitial connective tissue, proliferation of neuroglia and collections of fatty granular cells.

In his review of neuromyelitis optica, Goulden [10] discussed the autopsy findings in 14 cases. He described early demyelination of the optic nerves in a necrotic process that eventually caused complete destruction of the nerve fibers. Goulden found infiltration with round cells very common but neuroglial proliferation to form scar tissue uncommon. Abelsdorf [13c] discussed the findings in an interesting case in which the process extended through both optic nerves, the chiasm and the left optic tract; he expressed the belief that Devic's disease was a parenchymatous inflammation of the nerve tissue proper. In the pathologic discussion of his case, Beck [12] described massive demyelination of the cord and optic nerves and four types of cellular reaction: (1) round cell perivascular infiltration, (2) multiplication of blood vessels, (3) neuroglial proliferation and (4) polymorphonuclear cell infiltration of the tissues. In sections prepared by Bielschowsky's silver impregnation technic, Beck observed small areas of rarefaction in which even the axis-cylinders were destroyed; he expressed the belief that these lesions distinguished this disease from disseminated sclerosis. Michaux [30] decribed the three most likely sites for the initial lesion: (1) the upper dorsal segments of the cord, (2) the hypothalamic region and (3) the optic chiasm. Microscopically, Michaux observed the process to be essentially one of necrosis, the distinguishing features of which are (1) the irregularity of the lesions, (2) the intensity of the demyelination and (3) the destruction of axis-cylinders.

Balser,[18] reporting on the pathologic study of 3 cases of neuromyelitis optica, suggested that the lesions are initially perivascular and focal, and that they later extend or coalesce, so that there appears to be a central core of destruction. He stated that this process in the spinal cord tends to be continuous rather than spotty, often involving a number of consecutive segments in a linear lesion. Histologically, according to Balser, there are proliferation of blood vessels and infiltration of the tissues with lymphocytes, plasma cells and a few polymorphonuclear leukocytes; the axis-cylinders show thickening, fragmentation and end bulb formation. There is slight or no proliferation of neuroglial fibers in the early, nonremissive stage, Balser found; but a dense, fibrous connective tissue overgrowth may occur later in the disease. Cone, Russel and Harwood [16] reported intense glial scarring in their case, with the formation of dense plaques in the cerebrum and cerebellum. Markiewicz and Peters [45] commented particularly on the

TABLE 2.—*Pathologic Changes in 20 Cases with Autopsy*

Case No.	Author	Distribution of Lesions	Demyelination	Loss of Axis-Cylinders	Neuroglial Proliferation	Perivascular Infiltration	Proliferation of Capillaries	Cavitation
1	Beck	Optic nerves chiasm, optic tracts and spinal cord	"Massive"	+	Astrocytosis; some microglia; many gitter cells	Lymphocytes, polymorphonuclear cells, plasma cells, and gitter cells	Great multiplication	Optic nerves, tracts, chiasm, and spinal cord
2	Walsh	Cerebral cortex, basal ganglions, optic nerves, chiasma and spinal cord	"Intense"	+	"Slight"	"Minimum"	..	Spinal cord
3	Fralik and DeJong	Lumbar section of cord (only part examined)	"Complete"	"Complete"	"Countless microglia"	"None"	..	..
4	Balser (case 1)	Optic nerves, chiasm, geniculate bodies, hypothalamus and spinal cord	"Entire optic tract"	+	"Very little"	Lymphocytes, polymorphonuclear cells, and plasma cells	+	..
5	Balser (case 2)	Brain, optic tracts and spinal cord (optic nerves not obtained)	Present	+	None in the cerebrum, very little in the spinal cord	Lymphocytes, occasional polymorphonuclear cells and plasma cells	"Quite marked"	Spinal cord
6	Balser (case 3)	Spinal cord (only part examined)	"Diffuse"	+	"Very little"	Lymphocytes, polymorphonuclear cells, and plasma cells	+	..
7	Dolgopol	Spinal cord, medulla and optic nerves	"Extensive"	—	Some astrocytosis; little microglial reaction	Lymphocytes and plasma cells	..	..
8	Cone, Russel and Harwood	Brain, cerebellum, optic nerves, chiasm and spinal cord	Present	+	.....	Rare lymphocytes	..	Spinal cord
9	Noran and Polan	Optic nerves, spinal cord and lower part of medulla	"Extensive"	"Marked"	Astrocytes and microglia	Lymphocytes	+	Spinal cord
10	Kohut and Richter	Right optic nerve, lower part of medulla and spinal cord	"Severe, patchy"	+	Hyperplastic astrocytes and increased microglia	Lymphocytes, with some histiocytes	..	Spinal cord
11	Hassin	Right optic tract, right cuneus, internal capsule and spinal cord	Present	+	Some astrocytosis; great increase in microglia	Lymphocytes and gitter cells	"Many new capillaries"	..
12	Hurst, de Crespigny and Fry	Optic nerves, chiasm, optic tracts, geniculate bodies and spinal cord	"Extensive"	+	Great increase in microglia	Widespread lymphocytes	..	..
13	McAlpine (case 1)	Optic nerves and spinal cord	"Diffuse"	+	Moderate macroglial reaction; marked microglial reaction	None	"Slight increase"	..
14	McAlpine (case 2)	Optic nerves, chiasm, left optic tract, lower part of medulla and spinal cord	"Diffuse"	+	Moderate macroglial reaction; marked microglial reaction	Slight, lymphocytes	+	Spinal cord
15	Lowenberg, DeJong and Foster	Optic nerves, some of the spinal nerves and spinal cord	.....	+	Increase in the macroglia and microglia	Lymphocytes	+	+
16	Stansbury (case 1)	Optic nerves, lower part of medulla and spinal cord	Present	+	Moderate astrocytosis and a great increase in microglia	Lymphocytes, plasma cells and occasional monocyte	..	..
17	Stansbury (case 2)	Cerebral cortex (one small lesion), right optic nerve and spinal cord	"Massive"	+	Moderate astrocytosis and a great increase in microglia	Lymphocytes and plasma cells	..	..
18	Stansbury (case 3)	Right optic nerve, lower part of medulla and spinal cord	Present	+	Moderate astrocytosis and a great increase in microglia	Lymphocytes and plasma cells	..	Spinal cord
19	Stansbury (case 4)	Optic nerves and pons	"Extensive"	+	Moderate astrocytosis and a great increase in microglia	Lymphocytes, plasma cells and occasional monocyte	..	..
20	Stansbury (case 5)	Cerebral cortex, basal ganglions, brain stem, right optic nerve and spinal cord	Present	+	Moderate astrocytosis and a great increase in microglia	Lymphocytes, plasma cells and occasional monocyte	..	..

absence of gliosis in their case, while Putnam and Forster [27] stated that chronic glial fibrosis occurs frequently in neuromyelitis optica, in addition to the acute degenerative changes.

In a study of the pathologic changes in 12 cases of neuromyelitis optica, McAlpine [25] found diffuse myelitis in 9 cases and disseminated focal lesions in the remaining 3 cases. The hallmark of neuromyelitis optica, according to McAlpine, is necrosis, which in the cases with diffuse myelitis is sometimes accompanied with cavitation. He stated that the response of the macroglia depends on the intensity of the lesion; when necrosis occurs not even the astrocytes are spared, and then gliosis is impossible, except at the margins of the involved areas. On the other hand, McAlpine observed that the microglia uniformly show a pronounced reaction in the form of fat granule corpuscles; the microglial elements are able to perform this function because of their motility and rapid proliferation. In his experience, proliferation of capillaries is relatively uncommon, two incompatible conditions being necessary: (1) a duration of several months and (2) severe necrosis. When the capillary reaction does occur, McAlpine explained, it is because the destruction of astrocytes and consequent poor glial reaction leave only one tissue able to effect any repair, namely, the blood vessels.

Cerebral Lesions.—The lesions of neuromyelitis optica are not confined to the spinal cord and optic nerves in all cases; in fact, Devic was first to mention the occurrence of cerebral foci. Jumentié and Valiére-Vialeix [13g] described a case in which the pathologic process was centered in the brain; postmortem examination revealed a large area of softening in the left occipital lobe and numerous smaller foci in the right occipital lobe, with the characteristic changes in the optic nerves and cord. Bouchut and Dechaume [13j] reported a case with lesions in the spinal cord, medulla, midbrain, cerebellum and brain, in addition to those in the optic nerves. Guillain and associates [31p] also reported a case with pathologic cerebral changes; associated with lesions typical of neuromyelitis optica in the spinal cord and optic nerves, they noted a large necrotic area in the hypothalamic region. Demyelinated lesions in the cerebral cortex and brain stem were also described by Cestán, Riser and Planques [36] and by Alajouanine and associates.[38] Walsh,[17] too, found small lesions throughout the white matter of the brain and spinal cord; in his case practically all the white matter around the calcarine fissure was involved.

Review of the Pathologic Changes in 20 Cases.—In an attempt to better correlate the distribution of the lesions in neuromyelitis optica and to ascertain the distinctive features of these lesions, the pathologic features of the 15 cases previously discussed clinically were studied and the data combined with corresponding information for the 5 cases presented in this report. The data are presented in table 2.

Study of the pathologic picture in 20 cases reveals the following facts:

1. Distribution of the lesions was as follows:

	No. of Cases
Optic nerves (not obtained in 4 cases)	16
Optic chiasm	5
Optic tracts	5
Cerebral hemispheres	5
Brain stem	12
Spinal cord	19
Cerebellum	1

2. Demyelination was prominent in 19 cases. It was not specifically mentioned in the remaining case, apparently by an omission.

3. Destruction of axis-cylinders was described in 19 cases.

4. Astrocytosis, usually mild, was described in 13 cases. Proliferation of the microglia, usually pronounced, was noted in 15 cases. Neuroglial proliferation, without mention of cell type, was noted as "slight" in 1 case and as "very little" in 3 cases and was not mentioned in 1 case.

5. Perivascular infiltration of lymphocytes, polymorphonuclear leukocytes and plasma cells was noted in 4 cases; of lymphocytes and plasma cells in 5 cases; of lymphocytes and polymorphonuclear leukocytes in 1 case and of lymphocytes alone in 7 cases. No infiltration was noted in 2 cases and a "minimum" infiltration in another.

6. Proliferation of capillaries was described in 9 cases.

7. Cavitation (usually in the spinal cord) was present in 9 cases.

From this review of the autopsy observations in 20 cases, we may conclude, then, that neuromyelitis optica is characterized histologically by (1) demyelination of nerves, (2) destruction of axis-cylinders, (3) mild astrocytosis and pronounced proliferation of microglia, (4) perivascular infiltration of lymphocytes, plasma cells and sometimes polymorphonuclear leukocytes, (5) proliferation of capillaries and (6) cavitation. The lesions are commonly found in the optic pathway, spinal cord and brain stem, occasionally in the cerebral hemispheres and rarely in the cerebellum.

Composite View of Microscopic Pathology.—The pathologic process of neuromyelitis optica passes through a number of stages, during which the reaction of the nerve tissue changes from stage to stage. Thus, the microscopic picture will vary according to the stage of the lesion being studied. Some stages appear commoner because they last longer than others, so that an observer, without careful study of many lesions, may see only one or more stages of the pathologic process.

An erroneous opinion of the nature of the disease may thus be conceived. A misunderstanding of this sort concerning the pathology of multiple sclerosis existed for many years; pathologists, seeing mainly glial scars or plaques, were misled into thinking of multiple sclerosis as a primary overgrowth of the neuroglia. In the case of neuromyelitis optica, the microscopic picture is determined by three variables: (1) the severity of the reaction in the particular lesion, (2) the age of the lesion and (3) the portion of the lesion under study. All degrees

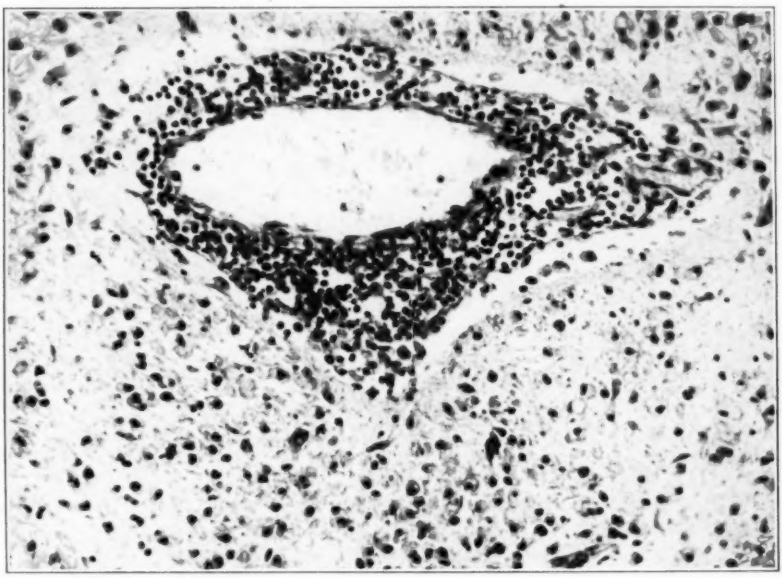


Fig. 11 (case 3).—Photomicrograph showing the typical perivascular collection of lymphocytes and plasma cells.

of severity are observed in different lesions, even in fatal cases. The age of the lesion is significant, because this process appears to run through a certain calendar of tissue reactions. Finally, the pathologic process varies within a single lesion, in that its intensity decreases from within outward. By the time the disease has caused the patient's death, most lesions are old and severe, and at autopsy many more such lesions will be found than lesions of the initial, early stage. Therefore, in order to give a better perspective of the whole process, a composite description of the microscopic events has been assembled, with photomicrographs from the 5 cases previously presented.

Acute Inflammatory Stage: The earliest lesion of neuromyelitis optica is an acute inflammatory process about a small blood vessel. As in inflammation elsewhere, there is exudation from the blood of fluid and leukocytes. The fluid causes edema of the sheaths of the vessel and of the tissue spaces of the surrounding parenchyma, making possible the infiltration of white blood cells. This infiltration is obviously a hematogenous one and is composed of polymorphonuclear leukocytes, lymphocytes and plasma cells. The polymorphonuclear cells are seen

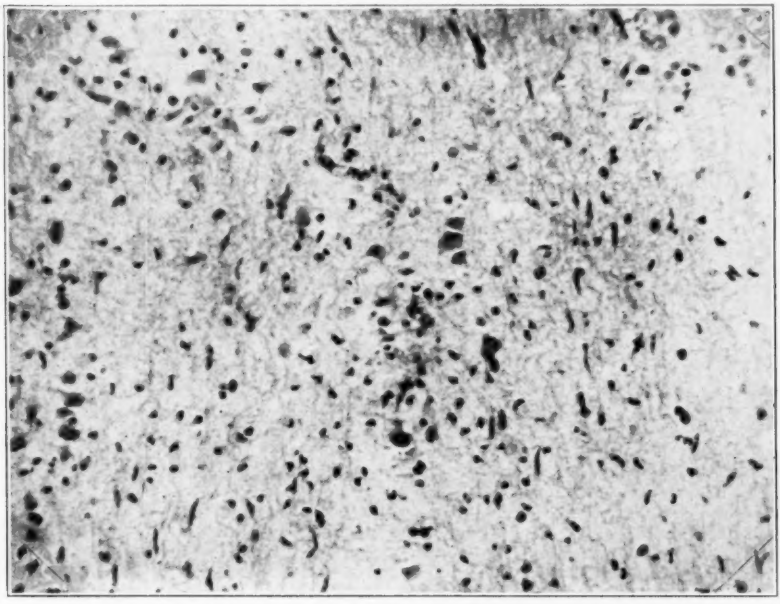


Fig. 12 (case 2).—Photomicrograph of a section of optic nerve, showing loss of the interstitial tissue between the nerve bundles and resulting disorganization of the normal architecture.

only in the earliest lesions; lymphocytes and plasma cells soon predominate, and perivascular lymph spaces packed with these cells (fig. 11) are seen throughout the nerve tissue in a case of neuromyelitis optica. As the process continues, the parenchyma farther from the vessel becomes edematous and begins to degenerate; the same cellular infiltration follows. Degeneration and cellular infiltration of the white matter may be seen between two blood vessels entering the cord; infiltration of the pia-arachnoid by the same cells can also be seen. In

the optic nerves, the interstitial tissue between the nerve bundles is involved very early, and the normal architecture of the nerve disappears (fig. 12).

Stage of Tissue Destruction: The first breakdown of nerve tissue is seen in the demyelination of the neurons in this small perivascular focus; figure 13 shows several of these small perivascular foci. In this stage of beginning demyelination, microscopic examination of one of the sections stained for myelin shows irregular swelling, fragmentation and partial loss of myelin in individual nerve fibers. As the

Fig. 13 (case 3).—Photomicrograph of a section of cerebral cortex, showing several small perivascular foci of demyelination and one large coalescent area. Mahon stain.

process continues, the neurons in this original focus become totally demyelinated, and the neurons farther away begin to lose their myelin. A characteristic lesion has a central perivascular core of complete demyelination; outside this is a diffuse zone of partial demyelination with some sheaths missing, some disintegrating sheaths and intact sheaths here and there. The margins of the lesion show a greater number of intact sheaths and fewer sheaths undergoing disintegration. Figure 14 illustrates these zones in a lesion of the optic nerve. The degree of demyelination varies directly with the severity of the proc-

ess; advanced lesions are recognized by the complete lack of staining with the myelin stains, while milder lesions contain numbers of neurons with intact sheaths passing through the softened area (fig. 14). The foci of demyelination vary greatly in size; often, large demyelinated areas cover the entire anterior or lateral white column in the spinal cord or the whole cross section of an optic nerve. On the other hand, there are always small, circumscribed lesions scattered irregularly throughout the spinal cord and optic system. Study of the demyelination explains the formation of the large lesions: As the disease pro-

Fig. 14 (case 2).—Photomicrograph of a section of optic nerve, showing the margin of a focus of demyelination. There is almost complete demyelination in the lower right corner, partial loss in the center and little loss of myelin to the left. Weil stain.

gresses, the original small perivascular foci spread out, coalesce and eventually form large, irregular lesions (fig. 13), with no obvious relation to blood vessels.

When the process is mild, the nerves may suffer no more damage than the loss of their myelin sheathing, but when it is severe the axis-cylinders are also destroyed. The latter possibility is the rule in neuromyelitis optica, however, and most lesions (stained appropriately) show edema, fragmentation and disintegration of axis-cylinders micro-

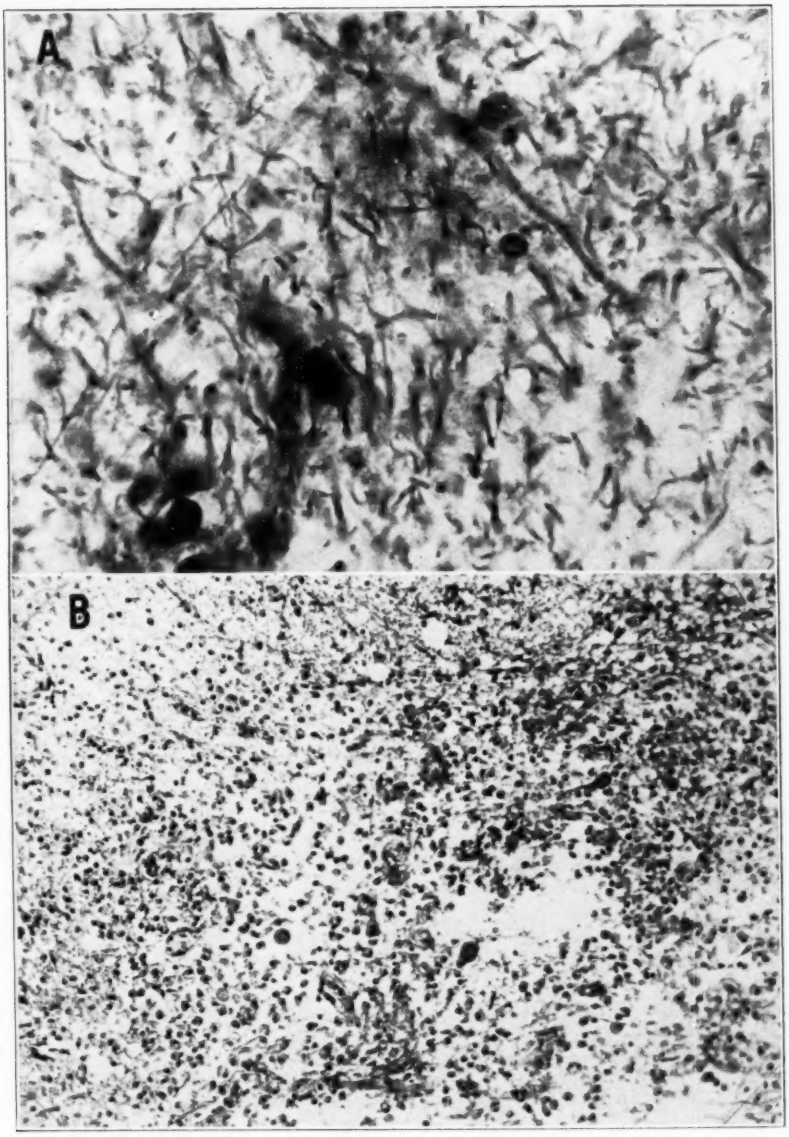


Fig. 15 (case 1).—*A*, photomicrograph of a section of the cord, showing advanced disintegration of axons and a great decrease in number; Bodian stain. *B*, photomicrograph of a section of the anterior gray horn of the cervical portion of the cord, showing more extensive necrosis, with total disappearance of the large nerve cells and clear areas, where all tissue elements have been destroyed.

scopically. The number of destroyed axis-cylinders varies directly with the amount of demyelination; in other words, both factors vary directly with the severity of the process. However, there are always more myelin sheaths lost than axis-cylinders; although many axons are destroyed, a good number are still preserved in the demyelinated foci. Even in the severest lesions, when all myelin sheaths have disappeared, many axis-cylinders are still to be seen. Some of the remaining axons, however, are swollen, distorted and degenerated (fig. 15*A*).

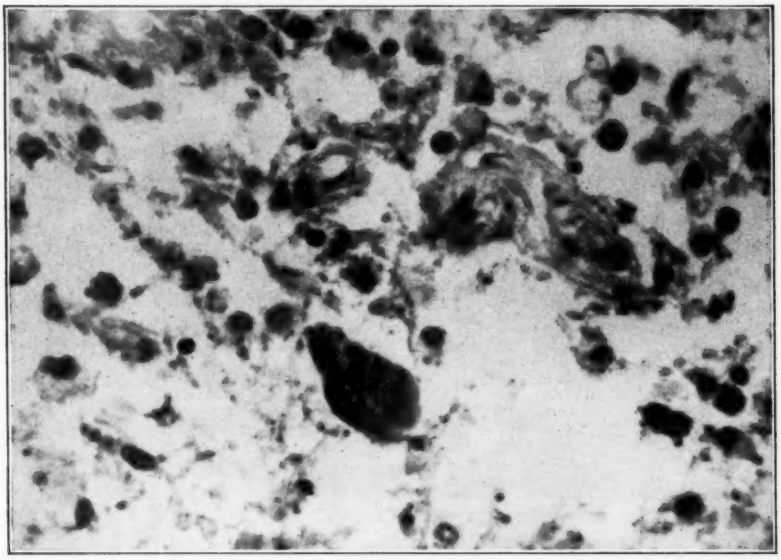


Fig. 16 (case 1).—Photomicrograph of a section of anterior gray horn from the spinal cord, showing advanced necrosis of nerve tissue. A swollen, pyknotic nerve cell is surrounded by the granular remains of interstitial tissue and by phagocytic microglia cells.

The pathology of neuromyelitis optica is not confined to the white matter of the nervous system; the same process, with similar destruction of nerve elements, is also seen in the gray matter. In the spinal cord, foci of destruction are common in the anterior and posterior gray horns. Here the large nerve cells become edematous and undergo chromatolysis. Their neurofibrils break up and agglutinate; there is solution of their Nissl substance. The abundant cytoplasm of these cells becomes fenestrated and vacuolated; the nucleus shrivels and disappears. Pyknosis and neuronophagia are seen; and the cell body

frequently becomes filled with degenerative lipid material. The end result is a pale-staining, vacuolated shell, usually deformed. When the process is toxic enough, complete disintegration and disappearance of the cell body occur (fig. 15 *B*). That this disease is not limited to the white matter is seen in the fact that lesions do not end at the junction of the white and the gray matter. Lesions in the white columns that happen to be located near the central gray matter often protrude into the gray substance or appear to send tongues of necrosis

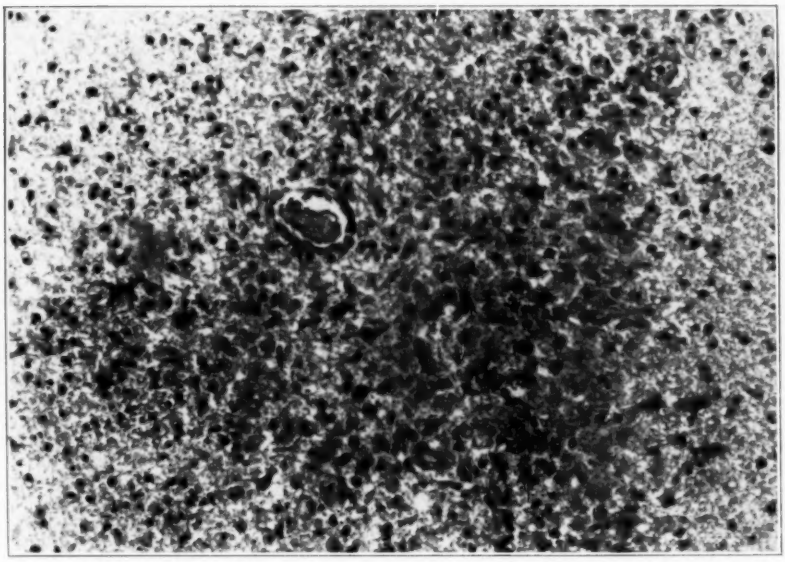


Fig. 17 (case 3).—Photomicrograph of a section of optic nerve, showing a collection of microglia cells in the process of multiplication and proliferation.

into the gray horns. Similarly, lesions situated initially in the central gray matter often bulge out into one of the encircling white columns.

The death of cells constitutes necrosis, and this is the end result in the lesions of neuromyelitis optica, when nerve cell bodies, axis-cylinders, myelin sheaths and interstitial tissue are destroyed. In these necrotic lesions, all degrees of destruction can be seen: fragmentation and disintegration of axons, globules of broken-down myelin, dying nerve cells and remnants of interstitial tissue. Degenerating astrocytes show clasmatodendrosis, and corpora amylacea, from hyalinization of astrocytes, are to be noted. The "scavenging" microglia cells, hyper-

trophied into fat-granule bodies, are everywhere ingesting fragments of myelin. Figure 16 is a highly magnified photomicrograph of severe necrosis in an anterior gray horn, showing the disintegrated granular remains of interstitial tissue, a swollen pyknotic nerve cell and phagocytic microglia cells. When necrosis occurs in tissue unable to replace the void by scar formation, or when it happens too fast for scarring, loss of substance is the inevitable result. As this vacuolation proceeds, the tissue assumes a cystic appearance. Finally, when microcystic

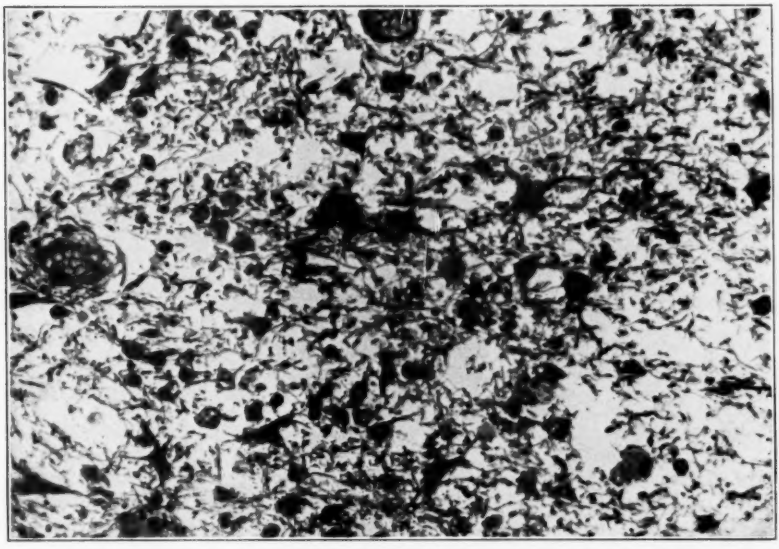


Fig. 18 (case 3).—Photomicrograph of a section of brain stem, showing proliferation of astrocytes in a degenerated area.

degeneration becomes severe enough and extensive enough, gross cavitation results, as seen in the spinal cord in case 5 (fig. 10).

Stage of Phagocytosis: The first response of the nervous system to this destructive process is the proliferation of the microglia. The microglia cells, considered by some to be part of the reticuloendothelial system, are mesodermal in origin; they are the counterpart of histiocytes in other parts of the body. The microglia cells multiply and hypertrophy, and when seen in collected masses at this stage (fig. 17) they resemble collections of phagocytes in any organ. They now constitute the actively mobile phagocytic cells of the central nervous system. The microglia cells now assume their scavenger function and ingest

myelin globules from the disintegrating myelin sheaths. They are now known as compound granule cells, fat-granule cells or gitter cells. These lipid-laden cells are characteristically seen in large numbers throughout the sections in cases of neuromyelitis optica. The microglia cells also phagocytose the degenerating astrocytes (clasmatodendrosis), the necrotic nerve cells (neuronophagia) and the remnants of the axons.

Healing Stage: The second response of the nerve tissue in neuromyelitis optica is a poor attempt at repair; this consists first of multiplication and hypertrophy of astrocytes (fig. 18). The astrocytes are

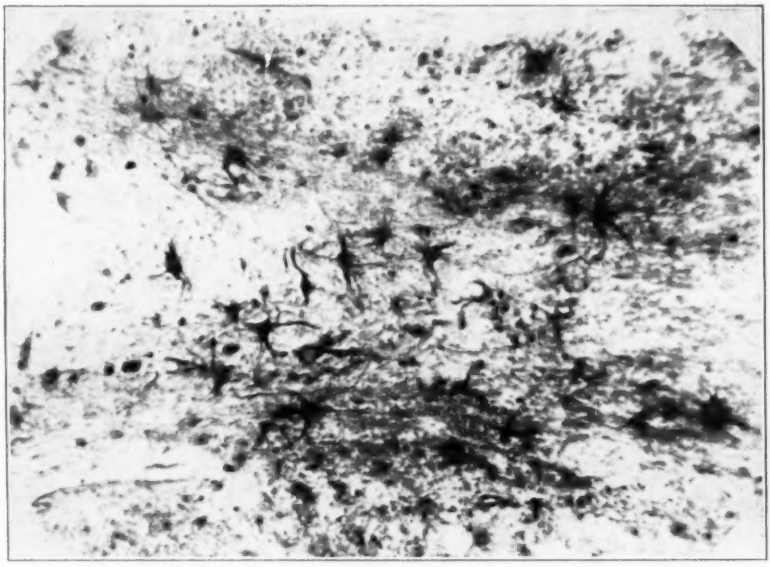


Fig. 19 (case 4).—Photomicrograph of a section of the right optic nerve, showing a group of astrocytes in an old inactive lesion.

the connective tissue cells of the central nervous system; they form the framework for the nerve tissue. Astrocytes may be compared to the cells of Müller in the retina; their cell bodies, likewise, lie within the stroma of the tissue and send out filamentous processes, with a foot plate at the termination, inward to form the internal limiting membrane of the central canal and ventricles and outward to form the external limiting membrane of the neuraxis. Because astrocytosis is reparative and secondary, and is seen after the subsidence of the acute inflammatory reaction, it is not prominent in the lesions of neuromyelitis optica, in which the patient usually dies in the acute stage of

the disease. In the early lesions, few or no astrocytes may be found; when they are seen, they are in the periphery of the necrotic area or in the healthy tissue just outside the lesion. (The normal complement of astrocytes at the site of a lesion are destroyed, with the other tissue elements.) In the older lesions, they are more prominent (fig. 19) as they grow into the necrotic focus to help the healing process, but astrocytes are never seen in great numbers as are the microglia.

The final reaction of the nervous system to the noxae of neuromyelitis optica is gliosis or scarring, by means of fibers laid down by

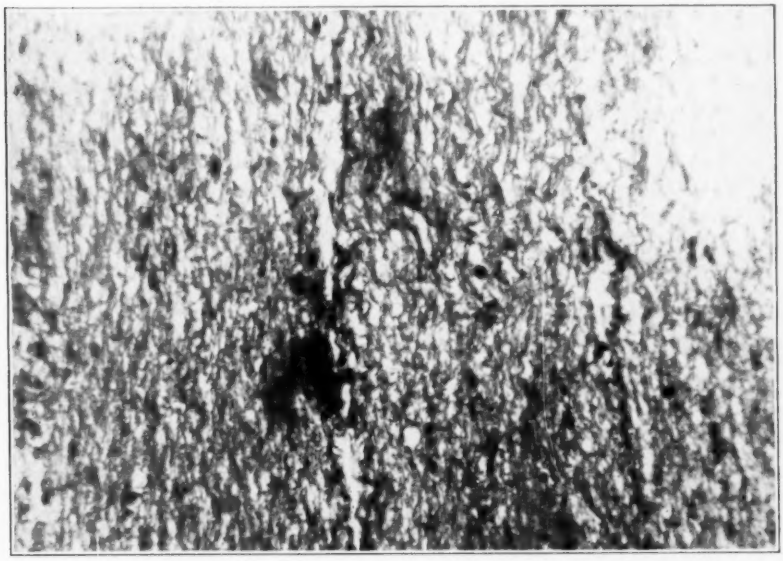


Fig. 20 (case 2).—Photomicrograph of a section of optic nerve, showing fairly dense gliosis.

the astrocytes. This is the connective tissue scar of the nerve tissue. It is seldom observed in this disease, and then only as partially formed glial scars. In 1 case of this study, however, a well developed scar was exhibited in one optic nerve (fig. 20).

ETIOLOGY

The earliest writers on neuromyelitis optica attempted to associate the optic neuritis with the pathologic process in the spinal cord by direct extension. Jones [71] hypothesized that injury to the spinal cord

71. Jones, W., cited by Allbutt.[2]

may involve the sympathetic nerves at their origin in the cervical segments and that the resulting irritation interferes with the vascular supply to the eye. Rieger and Forster [11d] elaborated Jones's theory, stating that the vasomotor paralysis produces first hyperemia and then atrophy of the optic nerves. Other investigators of that period, among them Allbutt,[2] concluded that optic neuritis following myelitis is caused by an ascending meningitis. Achard and Guinon [6] indicated alcohol as the cause in their case, as did Fuchs [8n] in his case. Dreschfeld [11l] stated the opinion that in most cases the condition follows the acute infectious diseases. Katz [11n] concluded that syphilis was the cause in 5 of the 15 cases he collected; in the remainder he attributed the disease to a poison with an affinity for the optic nerves and spinal cord. Cobbledick [72] attributed the disease in his case definitely to syphilis, and more recently Milian and associates [38] and Schaeffer [73] have stated that syphilis is a factor. Elschnig [11j] was first to suggest a noxious agent transmitted through the blood stream; later, Bielschowsky,[62] Strümpell [74] and Holden [60] endorsed this opinion.

Goulden,[10] impressed with the constancy of the clinical and pathologic picture, concluded that neuromyelitis optica is a specific infectious disease, an opinion with which Holmes,[75] Michaux,[30] Merkel [76] and Sager and Grigoresco [77] concurred. Holmes offered as proof of specific infection the fact that he had seen this syndrome in epidemic form in the British Expeditionary Forces in France in 1917. Jendralski [19b] reported a case in which he attributed the condition to a septic embolus originating from a paranephritic abscess. Raverdino [78] expressed the belief that the ocular complications of the spinal cord disease were due to increased intracranial pressure. Dedimos [79] reported 2 cases of the disease associated with malaria, in 1 of which improvement followed quinine therapy.

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72. Cobbledick, A. S.: A Case of Retrobulbar Neuritis Followed by Dorsal Myelitis, Ophthalmoscope **8**:12-24, 1910.

73. Schaeffer, H.: La neuropticomyélite aiguë, Bull. Soc. d'opht. Paris **9**:776-786, 1931.

74. Strümpell, A.: Ueber Myelitis, Neurol. Centralbl. **20**:415-417, 1901.

75. Holmes, G., in discussion on Beck,[12] pp. 702-703.

76. Merkel, K.: Ueber einen Fall sogenannter Neuromyelitis optica, Ztschr. f. d. ges. Neurol. & Psychiat. **129**:591-598, 1930.

77. Sager, O., and Grigoresco, D.: Beiträge zum Studium der Ophthalmoneuromyelitis und ihrer Beziehungen zur disseminierten Encephalomyelitis, Arch. f. Psychiat. **98**:378-387, 1932.

78. Raverdino, E.: Sulla nevrite ottica mielite transverso, Riv. oto-neuro-oftal. **1**:251-256, 1924.

79. Dedimos, P.: Les manifestations oculaires du paludisme, Arch. d'opht. **49**:166-180, 249-269 and 330-344, 1932.

For a number of years, a neurotropic virus was widely accepted as the cause of neuromyelitis optica, as well as of multiple sclerosis. For the former, a virus origin was particularly sponsored by Abelsdorf,[13e] Redliche,[80] Pette,[81] Paton,[59] Milian and associates [53] and Roger and associates.[82] Pette [81] said that optic neuromyelitis is likely to occur in epidemics of lethargic encephalitis and poliomyelitis. Later, Bouchut and Dechaume,[13j] Vedel and Puech [31k] and van Bogaert [31l] claimed that neuromyelitis optica is a part of the syndrome of epidemic encephalitis. The recent popularity of the virus theory is demonstrated by the fact that Hanes,[83] teaching a class of medical students in 1942, exhibited a case of neuromyelitis optica as a typical example of the virus diseases of the nervous system.

During the past decade, the idea has been repeatedly advanced that all the demyelinating diseases constitute a single disease process, with a variable symptomatology, due to different locations of the lesions. This concept arose originally from the similarity of neuromyelitis optica to multiple sclerosis in some cases, and the idea has since been expanded to include the other demyelinating diseases. Therefore, in any modern exposition of the etiology of neuromyelitis optica one must at least consider the "demyelinating disease group," the main subdivisions of which are (1) multiple sclerosis, (2) neuromyelitis optica, (3) Schilder's disease and its subdivisions and (4) the acute disseminated encephalomyelitides. At present, there are five principal theories of origin for these diseases.

1. *Infectious Theory.*—This theory was born in 1884 with the suggestion of Marie [84] that multiple sclerosis is caused by an infection of the central nervous system secondary to one of the acute infectious diseases (especially typhoid). Marie's theory, however, was soon forgotten, when Strümpell [85] in 1896 expressed the opinion that multiple sclerosis is due to an inherent tendency of the glia to overgrow and destroy the myelin sheaths; without any substantiation, this dictum was unaccountably accepted as fact for two decades. Then, in 1917,

80. Redliche, E.: Ueber ein gehäuftes Auftreten von Krankheitsfällen mit den Erscheinungen einer Enzephalomyelitis disseminata, Monatschr. f. Psychiat. u. Neurol. **64**:152-184, 1927.

81. Pette, H.: Ueber lokalisierte, unter dem Bilde eines raumbeschränkenden Prozesses verlaufende Spinalmeningitis, Arch. f. Psychiat. **74**:631-640, 1925.

82. Roger, H.; Opin, T., and Sedán, J.: Neuropticomyélite aiguë avec précession de légers troubles médullaires, Rev. d'oto-neuro-opht. **8**:12-16, 1930.

83. Hanes, F. M.: Neuromyelitis Optica: Deficiency States; Actinomycosis, Internat. Clin. **1**:207-215, 1942.

84. Marie, P.: Sclérose en plaques et maladies infectieuses, Progrès méd. **12**:287-289, 1884.

85. Strümpell, A.: Zur Pathologie der multiplen Sklerose, Neurol. Centralbl. **15**:961-964, 1896.

Kuhn and Steiner [86] announced the discovery of a spirochete (Spirochaeta argentinensis) in experimental animals inoculated with the spinal fluid of patients with multiple sclerosis. Subsequently, Siemerling,[87] Büscher,[88] Speer [89] and Schuster [90] claimed to have demonstrated this spirochete in human beings with multiple sclerosis. On the other hand, Birley and Dudgeon,[91] Stevenson [92] and Noguchi and Collins [93] were unable to find the organism, and Lüthy [94] soon showed that these "spirochetes" were only fragments and distortions of impregnated axis-cylinders.

The theory of the virus origin of the demyelinating diseases began in 1913, when Bulloch [95] paralyzed rabbits with injections of spinal fluid from patients with multiple sclerosis and concluded that a filtrable virus was the responsible agent. In 1930 Chevassut [96] and Purves-Stewart [97] announced the isolation of the virus of multiple sclerosis (Spherula insularis); they prepared an autogenous vaccine from the virus and reported [98] favorable results from its administration to patients with active multiple sclerosis. However, Lépine and Mollaret [99]

86. Kuhn, P., and Steiner, G.: Ueber die Ursache der multiplen Sklerose, Klin. med. **13**:1007-1009, 1917.

87. Siemerling, E.: Spirochäten im Gehirn eines Falles von multipler Sklerose, Klin. Wchnschr. **55**:273-274, 1918.

88. Büscher, J.: Spirochätenbefund bei multipler Sklerose: Ein Beitrag zur Pathogenese, Arch. f. Psychiat. **62**:426-440, 1920.

89. Speer, E.: Spirochätenbefund im menschlichen Zentralnervensystem bei multipler Sklerose, München med. Wchnschr. **68**:425-426, 1921.

90. Schuster, J.: Ein Fall von multipler Sklerose mit positivem Spirochätenbefund, Ztschr. f. d. ges. Neurol. u. Psychiat. **73**:433-436, 1921.

91. Birley, J. L., and Dudgeon, L. S.: A Clinical and Experimental Contribution to the Pathogenesis of Disseminated Sclerosis, Brain **44**:154-212, 1921.

92. Stevenson, G. S.: Spirochete Stain in Multiple Sclerosis, Arch. Neurol. & Psychiat. **9**:88-89 (Jan.) 1923.

93. Noguchi, H., and Collins, J.: An Experimental Study of Multiple Sclerosis: II. Experimental Results in Animals Inoculated with Blood and Cerebrospinal Fluid; Clinical History and General Discussion, J. A. M. A. **81**:2110-2112 (Dec. 22) 1923.

94. Lüthy, F.: Zur Frage der Spirochätenbefunde bei multipler Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **128**:290-294, 1930.

95. Bulloch, W. E.: The Experimental Transmission of Disseminated Sclerosis to Rabbits, Lancet **2**:1185-1186, 1913.

96. Chevassut, K.: The Etiology of Disseminated Sclerosis, Lancet **1**:552-560, 1930.

97. Purves-Stewart, J.: A Specific Vaccine Treatment in Disseminated Sclerosis, Lancet **1**:560-564, 1930.

98. Purves-Stewart, J.: Disseminated Sclerosis: Experimental Vaccine Treatment, Lancet **1**:1072-1073, 1930.

99. Lépine, P., and Mollaret, P.: Recherches sur l'étiologie de la sclérose en plaques, Bull. Acad. de méd., Paris **105**:512-518, 1931.

and Tronconi [100] immediately reported the observation of this spherule in the spinal fluid in other diseases. Hicks and Hocking [101] repeated Chevassut's work and concluded that the spherule was not a virus but a precipitation phenomenon found in many other conditions. The virus theory has not been discarded, however, and reports of the isolation of the virus still appear in the literature.[102]

The infectious theory of causation has received support from the fact that acute disseminated encephalomyelitis following various infectious diseases (measles, scarlet fever, chickenpox) and certain prophylactic measures (the Pasteur treatment, administration of tetanus antitoxin) possesses a demyelinating process similar to that of multiple sclerosis and neuromyelitis optica. Clinically, the significant fact is that the encephalitis occurs late in the course of a virus disease; this has, of course, led many to think that the encephalitis is a manifestation in the nervous system of the virus producing the initial disease. Attempts to recover the virus from the nerve tissue, however, have been unsuccessful. It has also been observed that this encephalitis occasionally follows a disease not caused by a virus, and this observation led to the proposal that an unknown neurotropic virus is activated by many diseases, but especially by virus diseases. The fact remains, however, that no virus has yet been demonstrated that will produce the typical demyelinating lesion, either in man or in an experimental animal (Rivers,[103] Hurst [19]).

2. *Toxic Theory.*—Over fifty years ago, Oppenheim,[104] noting that some of his patients with multiple sclerosis were exposed occupationally to lead intoxication, attributed the lesions of that disease to lead as a toxic substance. This hypothesis was revived in 1932, when Hallervorden [105] compared the concentric rings of demyelination of Baló [106] with the Liesegang chemical phenomenon and suggested that multiple sclerosis may similarly be caused by the diffusion of a toxin

100. Tronconi, V.: Sulla etiologica della sclerosi in placche: Ricerche sulla cosidetta "spherula insularis," Boll. Soc. med.-chir., Pavia **45**:355-359, 1931.

101. Hicks, J. A. B., and Hocking, F. D. M.: Observations on a Spherule Recently Described in Disseminated Sclerosis, Lancet **2**:401-402, 1931.

102. Margulis, M. S.; Soloviev, V. D., and Shubladze, A. K.: Etiology and Pathogenesis of Acute Sporadic Disseminated Encephalomyelitis and Multiple Sclerosis, J. Neurol., Neurosurg. & Psychiat. **9**:63-74, 1946.

103. Rivers, T. M.: Relation of the Filtrable Viruses to Diseases of the Nervous System, Arch. Neurol. & Psychiat. **28**:757-777 (Oct.) 1932.

104. Oppenheim, H.: Zur Lehre von der multiplen Sklerose, Klin. Wchnschr. **33**:184-189, 1896.

105. Hallervorden, J.: Zur Pathogenese der multiplen Sklerose und ein Vorschlag zur Therapie, München. med. Wchnschr. **79**:602-604, 1932.

106. Baló, J.: Encephalitis Periaxialis Concentrica, Arch. Neurol. & Psychiat. **19**:242-264 (Feb.) 1928.

from a central point in the brain (lateral ventricles). Clinically, the toxic theory has been supported by reports of demyelination produced by various toxic agents: carbon monoxide (Hilpert [107]), lead (Cone, Russel and Harwood [15]), cadmium (Hadden [108]) and arsenic (Ecker and Kernohan [109]). Experimentally, demyelinated lesions have been produced in laboratory animals by a number of toxic substances: tetanus toxin (Claude,[110] Putnam [111]), saponin (Donaggio [112]), cobra venom and streptocolysin (Weil [113]), carbon monoxide (Putnam and associates,[114] and Yant and associates [115]), bile (Weil and Crandall [116]) and potassium cyanide (Ferraro,[117] Hurst [118]).

3. *Lipolytic Theory.*—That multiple sclerosis is caused by an enzyme that destroys lecithin was first suggested by Marburg [119] in 1906. In 1930 Brickner [120] investigated this theory in the laboratory; he found that plasma from patients with multiple sclerosis causes

107. Hilpert, P.: Kohlenoxydvergiftung und multiple Sklerose, Arch. f. Psychiat. **89**:117-130, 1929.

108. Hadden, S. B., in discussion on Lowenberg, K.; DeJong, R. N., and Foster, D. B.: Neuromyelitis Optica: Its Relation to Progressive Necrosis of Spinal Cord and Acute Multiple Sclerosis, Tr. Am. Neurol. A. **67**:59-66, 1941.

109. Ecker, A. D., and Kernohan, J. W.: Arsenic as a Possible Cause of Subacute Encephalomyelitis, Arch. Neurol. & Psychiat. **45**:24-43 (Jan.) 1941.

110. Claude, H.: Myélite expériementale sub-aiguë par intoxication tétanique, Arch. physiol. norm. et path. **9**:843-847, 1897.

111. Putnam, T. J.: Acute Multiple Sclerosis in Dogs, Arch. Neurol. & Psychiat. **24**:640-641 (Sept.) 1930.

112. Donaggio, A.: Sur le parkinsonisme post-encéphalitique: une doctrine corticonigrique, Rev. neurol. **43**:1058-1059, 1925.

113. Weil, A.: The Effect of Hemolytic Toxins on Nervous Tissue, Arch. Path. **9**:828-842 (April) 1930.

114. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591-1596 (Nov. 28) 1931.

115. Yant, W. P.; Chornyak, J.; Schrenck, H. H.; Patty, F. A., and Sayers, R. R.: Studies in Asphyxia, Public Health Bulletin 211, United States Treasury Department, Public Health Service, 1934, p. 61.

116. Weil, A., and Crandall, L. A.: Die Beziehungen zwischen dem Lipasezehalt und der neurotoxischen Wirkung des Serums nach experimenteller Leberschädigung, Ztschr. f. d. ges. Neurol. u. Psychiat. **140**:577-592, 1932.

117. Ferraro, A.: Experimental Toxic Encephalomyelopathy (Diffuse Sclerosis Following Subcutaneous Injections of Potassium Cyanide), Psychiat. Quart. **7**:267-283, 1933.

118. Hurst, W. E.: Experimental Demyelination of the Central Nervous System: I. The Encephalopathy Produced by Potassium Cyanide, Australian J. Exper. Biol. & M. Sc. **18**:201-223, 1940.

119. Marburg, O.: Die sogennante akute multiple Sklerose, Jahrb. f. Psychiat. **27**:213-312, 1906.

120. Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715-726 (April) 1930.

demyelination in the spinal cord of rats. Brickner hypothesized an enzymatic lipase as the cause of this disease. Then Brickner [121] tested the lipolytic power of serum from patients with multiple sclerosis to hydrolyze certain esters; he found that the blood serums from these patients shows higher lipolytic activity than normal blood serum and cited this finding as additional proof of his theory. However, Crandall and Cherry [122] showed that this lipase is also obtainable in equal amounts in patients with hepatic disease and, in lesser amounts, in many other conditions. Weil and Cleveland[123] repeated Brickner's experiments and agreed that the serum from patients with multiple sclerosis has an abnormally destructive action on the spinal cord of rats, but they also produced this destruction with serums from patients with other diseases. In 1935 Weil and Luhan [124] demonstrated a myelolytic substance in the urine of patients with multiple sclerosis, but, again, the enzymatic material was found in other conditions.

4. *Theory of Vascular Obstruction.*—That vascular occlusion is a factor in the pathogenesis of multiple sclerosis was suggested long ago (Rindfleisch,[125] Ribbert [126]); but thrombi, when present, have generally been considered one of the secondary changes produced by the disease. In 1928 Meyer [127] claimed priority in the production of demyelinated lesions by means of vascular occlusion. In 1931 Putnam and associates [114] repeated Meyer's experiments and found that a small minority of the animals showed demyelinated lesions surrounding a thrombosed vessel. Putnam [128] stated that the histologic changes produced by obstructive agents were so similar to the lesions of multiple sclerosis

121. Brickner, R. M.: Studies of the Pathogenesis of Multiple Sclerosis: III. Further Evidence of Abnormal Lipolytic Activity in the Blood in Multiple Sclerosis, Bull. Neurol. Inst. New York **2**:119-133, 1932.

122. Crandall, L. A., Jr., and Cherry, I. S.: Presence of an Olive Oil Splitting Lipase in the Blood of Patients with Multiple Sclerosis, Proc. Soc. Exper. Biol. & Med. **28**:572-574, 1931; Blood Lipase, Diastase, and Esterase in Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:367-374 (Feb.) 1932.

123. Weil, A., and Cleveland, D. A. A.: A Serologic Study of Multiple Sclerosis, Arch. Neurol. & Psychiat. **27**:375-388 (Feb.) 1932.

124. Weil, A., and Luhan, J. A.: The Demonstration of Myelolytic Substances in the Urine of Patients with Disseminated Sclerosis, Arch. Neurol. & Psychiat. **34**:459-461 (Aug.) 1935.

125. Rindfleisch, E.: Histologisches Detail zu der graven Degeneration von Gehirn und Rückenmark, Virchows Arch. f. path. Anat. **26**:474-483, 1863.

126. Ribbert, H.: Ueber multiple Sklerose des Gehirns und Rückenmarks, Virchows Arch. f. path. Anat. **90**:243-260, 1882.

127. Meyer, A.: Experimentelle Erfahrungen über die Kohlenoxydvergiftung des Zentralnervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:187-212, 1928.

128. Putnam, T. J.: Studies in Multiple Sclerosis: IV. "Encephalitis" and Sclerotic Plaques Produced by Venular Obstruction, Arch. Neurol. & Psychiat. **33**:929-940 (May) 1935.

that venular obstruction must be an essential antecedent to plaque formation. Later, Putnam [129] claimed to have demonstrated thrombi in human cases of encephalitis and multiple sclerosis and concluded that the primary factor in these diseases is to be found in the clotting mechanism of the blood. In 1943 Scheinker [130] studied the pathologic collection at the Salpétrière and corroborated Putnam's hypothesis of plaque formation about small venous thromboses.

On the other hand, Dattner [131] found that the clotting time of the blood was lengthened in many cases of multiple sclerosis. Dow and Berglund [132] in 1942, in a meticulous study of serial sections of 60 plaques, noted no signs of thrombosis in 51 of the lesions; in the remaining 9 lesions the observations were indecisive. These authors expressed doubt that thrombi sufficiently large to produce these plaques could disappear without a trace. In 1946 Reese,[133] reporting the use of an anticoagulant drug, dicumarol® (3,3-methylenebis 4-hydroxycoumarin), in 28 cases of multiple sclerosis, found no objective improvement in any of his cases.

Recently, Franklin and Brickner [134] suggested that the lesions of multiple sclerosis are caused by vasospasm of the smaller arterial vessels. Studying the retinal arterioles in 18 patients with this disease, they found scotomas associated with arteriolar constrictions and were able to reduce both the constrictions and the size of the scotomas with vasodilators. Franklin and Brickner could not explain the cause of the vasospasms.

5. *Allergic Theory.*—The allergic theory for the demyelinating diseases evolved from the persistent reports in the literature of encephalitis, encephalomyelitis and myelitis following the administration of various serums and vaccines, especially vaccination and the Pasteur treatment.

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129. Putnam, T. J.: Evidences of Vascular Occlusion in Multiple Sclerosis and "Encephalomyelitis," Arch. Neurol. & Psychiat. **37**:1298-1321 (June) 1937. Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: A Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, ibid. **41**:1087-1110 (June) 1939.

130. Scheinker, I. M.: Histogenesis of the Early Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **49**:178-185 (Feb.) 1943.

131. Dattner, B.: Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **37**:1221 (June) 1937.

132. Dow, R. S., and Berglund, G.: Vascular Pattern of Lesions of Multiple Sclerosis, Arch. Neurol. & Psychiat. **47**:1-18 (Jan.) 1942.

133. Reese, H. H.: What Do We Know About Multiple Sclerosis? Journal-Lancet **66**:359-362, 1946.

134. Franklin, C. R., and Brickner, R. M.: Vasospasm Associated with Multiple Sclerosis, Arch. Neurol. & Psychiat. **58**:125-162 (Aug.) 1947.

Bassoe and Grinker,[135] Gayle and Bowen,[136] Kraus and Chaney,[137] Scheinker [138] and many others have reported encephalomyelitis following immunization procedures. In 1929 Foster Kennedy [139] was the first in this country to draw attention to the occasional encephalopathy following the use of foreign serums. Since that time, Allen,[140] Doyle [141] and Winkelman and Gotten [142] have discussed encephalomyelitis following serum therapy. Glanzmann [143] was first actually to attribute these nervous complications to allergy. This concept was evidently engendered by the fact that a period, approximately comparable to that required for the development of sensitivity to a foreign protein, usually elapses between the administration of the vaccine or serum and the onset of the complicating encephalitis. Kennedy,[144] denying the existence of any proof of the allergic theory, at the same time admitted that the clinical events of these processes in the central nervous system resemble multiple sclerosis and that the pathologic features are also suggestively similar.

In 1937 Ferraro [85] published a comprehensive review of the pathology of the demyelinating diseases, in which he attempted to prove that these diseases are allergic reactions of the nervous system because of the similarity of their pathology to that of experimental anaphylaxis in laboratory animals. Ferraro listed as the essential pathologic features of these conditions (1) perivascular demyelination, (2) hemorrhages, (3) degeneration of the walls of the blood vessels, (4) thrombus formation, (5) perivascular cellular infiltration, (6) giant cells, (7) necrosis and (8) gliosis. According to Ferraro, interpretation of this pathologic

135. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis, Arch. Neurol. & Psychiat. **23**:1138-1160 (April) 1930.

136. Gayle, R. F., and Bowen, R. H.: Acute Ascending Myelitis Following the Administration of Typhoid Vaccine: Report of a Case with Necropsy Findings, J. Nerv. & Ment. Dis. **78**:221-231, 1933.

137. Kraus, W. M., and Chaney, L. B.: Serum Disease of the Nervous System, Arch. Neurol. & Psychiat. **37**:1035-1047 (May) 1937.

138. Scheinker, I. M.: Disseminated Encephalomyelitis and Its Relation to Multiple Sclerosis, J. Neuropath. & Exper. Neurol. **2**:418-419, 1943.

139. Kennedy, F.: Certain Nervous Complications Following the Use of Therapeutic and Prophylactic Sera, Am. J. M. Sc. **177**:555-559, 1929.

140. Allen, I. M.: The Neurological Complications of Serum Treatment, Lancet **2**:1128-1131, 1931.

141. Doyle, J. B.: Neurologic Complications of Serum Sickness, Am. J. M. Sc. **185**:484-492, 1933.

142. Winkelman, N. W., and Gotten, N.: Encephalomyelitis Following the Use of Serum and Vaccine, Am. J. Syph. & Neurol. **19**:414-424, 1935.

143. Glanzmann, E.: Die nervösen Komplicationen der Varizellen, Variola, und Vakzine, Schweiz. med. Wchnschr. **57**:145-154, 1927.

144. Kennedy, F.: Allergy and Its Effects on the Central Nervous System, J. Nerv. & Ment. Dis. **88**:91-100, 1938.

change as an allergic reaction does not exclude the thrombus theory of Putnam; the basic process may be an allergic thrombus formation. In addition to thrombosis, Ferraro stated that allergy may cause vascular obstruction by vasospasm, by changing the coagulation time of the blood and by causing periarteritis or intimal hyperplasia.

Finley [145] in 1938 discussed allergy as a factor in the encephalitis associated with vaccination, variola and measles; he recalled that the expanding vaccinia reaction (eighth to twelfth days) represents the reaction between antibodies then forming and the virus in the papule. According to Finley, this reaction occurs all over the body, giving rise to local or general exanthems (if they occur) at this time, and also to the cerebral complications in about 90 per cent of cases. He concluded that the nervous complications represent an allergic response of nervous system to the virus of the exanthem. Baer and Sulzberger,[146] stating the belief that the allergic theory is based on circumstantial evidence, looked for another common form of allergy, atopic hypersensitivity, in 40 cases of multiple sclerosis. They were able to demonstrate it in only 10 cases, an incidence they considered not significantly higher than that in the general population.

Experimental Evidence for the Allergic Theory: First, it was obvious that the demonstration of brain-specific antigens was necessary to the hypothesis of encephalopathy caused by an antigen-antibody reaction. This proof was accomplished by Heimann and Steinfeld [147] and Plaut and Kassowitz [148] twenty years ago; these workers found that heterologous brain tissue was specific when injected into rabbits. Normal homologous brain is not antigenic, but Schwentker and Rivers [149] showed that autolysis or disease (vaccination) may so alter the tissues as to render them antigenic. Rivers and Schwentker [150]

145. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047-1054 (May) 1938.

146. Baer, R. L., and Sulzberger, M. B.: Role of Allergy in Multiple Sclerosis: Incidence of Atopy in a Series of Forty Cases, Arch. Neurol. & Psychiat. **42**:837-841 (Nov.) 1939.

147. Heimann, F., and Steinfeld, J.: Ueber das Verhalten der Hirnlipoide und ihrer Antisera, Ztschr. f. Immunitätsforsch. u. exper. Therap. **58**:181-192, 1928.

148. Plaut, F., and Kassowitz, H.: Ueber die Entstehung von Hirnantikörpern bei der Immunisierung normaler und syphilitischer Kaninchen mittels Hirnsuspensionen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **63**:428-439, 1929.

149. Schwentker, F. F., and Rivers, T. M.: The Antibody Response of Rabbits to Injections of Emulsions and Extracts of Homologous Brain, J. Exper. Med. **60**:559-574, 1934.

150. Rivers, T. M., and Schwentker, F. F.: Encephalomyelitis Accompanied by Myelin Destruction Experimentally Produced in Monkeys, J. Exper. Med. **61**:689-702, 1935.

then produced demyelinated lesions in monkeys with extracts of rabbit brain. Ferraro and Jervis [151] were successful in producing progressive neurologic signs in monkeys inoculated with rabbit brain; pathologically, they demonstrated lesions somewhat similar to those of the demyelinating diseases.

Anaphylaxis, an available laboratory procedure, has also been investigated for elucidation of any relation between allergy and the demyelinating diseases; similarity of the pathology of the Arthus phenomenon opened an easy avenue for laboratory exploration. Davidoff and associates [152] produced sensitivity in the brains of rabbits and then demonstrated local anaphylaxis of brain tissue at the site of antigen inoculation that was similar to the Arthus phenomenon seen in the skin. Kopeloff and associates [153] produced fatal anaphylaxis at will in monkeys by employing larger doses of the antigen. Alexander and Campbell [154] have demonstrated the Arthus phenomenon in the brains of guinea pigs. Using Forssman antibodies that cause demonstrable damage to capillaries, Jervis [155] produced demyelinated lesions about damaged capillaries in guinea pig brains and claimed that he had produced demyelinated lesions at the site of an antigen-antibody reaction. Other investigators have been unable to produce these demyelinated lesions; Dechaume and Croizat,[156] Garçin and Bertrand,[157] Baginski and associates [158] and Stief and Tokay [159] have all described anaphylactic lesions in the nervous system, in none of which demyelination appeared to be a feature.

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151. Ferraro, A., and Jervis, G. A.: Experimental Disseminated Encephalopathy in the Monkey, Arch. Neurol. & Psychiat. **43**:195-209 (Feb.) 1940.

152. Davidoff, L. M.; Seegal, B. C.; and Seegal, D.: The Arthus Phenomenon: Local Anaphylactic Inflammation in the Rabbit Brain, J. Exper. Med. **55**: 163-168, 1932.

153. Kopeloff, N.; Davidoff, L. M., and Kopeloff, L.: General and Cerebral Anaphylaxis in the Monkey (Macacus Rhesus), J. Immunol. **30**:477-485, 1936.

154. Alexander, L., and Campbell, A. C. P.: Local Anaphylactic Lesions of the Brain in Guinea Pigs, Am. J. Path. **13**:229-248, 1937.

155. Jervis, G. A.: Forssman's "Carotid Syndrome": A Contribution to the Study of Anaphylactic Changes in the Nervous System from the Standpoint of Pathology, Arch. Path. **35**:560-570 (April) 1943.

156. Dechaume, J., and Croizat, P.: Lésions nerveuses dans l'anaphylaxie chronique expérimentale, Compt. rend. Soc. de biol. **101**:1145-1146, 1929.

157. Garcin, R., and Bertrand, I.: Étude expérimentale des lésions du névraxe consécutives aux chocs anaphylactiques répétés et aux injections réitératives espacées d'albumine étrangère: Sur quelques considérations pathogéniques applicables à la neuro-pathologie humaine, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:787-796, 1935.

158. Baginski, S.; Czarnecki, E., and Hurynawicz, J.: Lésions histologiques du système nerveux des lapins en état anaphylactiques, Compt. rend. Soc. de biol. **130**:567-569, 1939.

159. Stief, A., and Tokay, L.: Durch experimentelle Serumanaphylaxie verursachte Veränderungen des Nervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **150**:715-728, 1934.

Comment.—1. The infectious theory, the oldest and most popular, has never been substantiated. The spirochetal hypothesis has been abandoned. Chevassut's organism has been discredited. The virus theory still has many proponents and remains a definite possibility. Against the virus theory is the argument that none of the known neurotropic viruses produce the demyelinating type of lesion.

2. The evidence in favor of the toxic theory appears weak. A few cases of multiple sclerosis and neuromyelitis optica have been found in association with poisoning by lead, arsenic and other metals. However, such cases are rare occurrences in the total number of such intoxications, and no relation in these instances has ever been proved except that of coincidence. The production of experimental demyelination by means of toxic substances is invalidated by the questionable similarity of the lesions to the pathologic process in man and by the fact that similar lesions are produced by so many other, nontoxic, agents.

3. The enzyme hypothesis of Brickner has not been accepted. His laboratory procedures and his interpretation of results have been criticized. Other investigators have shown that similar enzymatic substances are present in a number of other diseases.

4. The theory of vascular obstruction advocated by Putnam rests on his claims that he has produced "multiple sclerosis" in animals by occlusion of blood vessels, and that he has consistently demonstrated vascular thromboses in the lesions in man. The main arguments against these claims are (1) the failure of other pathologists to find the thromboses in cases of human multiple sclerosis, (2) the fact that Putnam's experimental lesions are not accepted as similar to the human type, (3) the demonstration of increased clotting time in multiple sclerosis and (4) the failure of anticoagulant therapy clinically.

5. The allergic theory of Ferraro depends on the production of similar lesions in laboratory animals by experimental anaphylaxis, and on the fact that acute encephalomyelitis occasionally follows the administration of serums and vaccines. Opposed to this view are these facts: (1) Many workers have been unable to reproduce Ferraro's results; (2) the experimental lesions do not closely resemble the lesions in man; (3) similar demyelinating lesions are also produced by many other, nonallergic, agents, and (4) the acute encephalomyelitides are not very common in view of the millions of vaccinations and serum injections.

It appears that the importance of demyelination is being overstressed in the search for the cause of the demyelinating diseases. Study of the literature concerning experimental demyelination reveals that a great number of widely different stimuli will cause the destruction of myelin

sheaths. Demyelination is, in fact, one of the first reactions of nerve tissue to trauma, and the injury apparently need not be specific. It has been shown that even minute pressure on a nerve will produce permanent demyelination (Denny-Brown and Brenner [160]). This suggests that the production of demyelination under experimental conditions does not necessarily contribute a clue to the etiology of any human disease.

It will be seen that most of the efforts to establish the etiology of the demyelinating diseases fall into three categories: (1) demonstration of the causative agent or process in man (spirochete, virus, enzyme, thromboses); (2) demonstration of the coincidence of a demyelinating disease and another condition (typhoid, lead poisoning, virus infection), and (3) experimental production of similar lesions in laboratory animals (by a wide variety of noxae). Most workers today are striving to attain the last-named goal (reproduction of similar lesions). This appears to be an attempt to prove what may well be a fallacy, because the demonstration of a similar pathologic process will not prove a similar etiologic agent. Pathologists may work out the histologic picture of a disease, but that gives them no license to draw conclusions as to the cause of the process. There are many identical lesions in the field of pathology that may be caused by two or more agents. The central nervous system, particularly, is so constructed that it can react to injury in only a limited number of ways. There are, therefore, only a certain number of pathologic pictures possible, regardless of the number of exciting agents. How, then, can any one agent causing experimental necrosis in the nervous system of animals, similar to the necrosis of neuromyelitis optica and multiple sclerosis, be necessarily indicted as the cause of these diseases? If this were possible, it would furnish a convenient "short-cut" to the satisfaction of Koch's postulates.

DIFFERENTIAL DIAGNOSIS

A large majority of physicians who have encountered a case of neuromyelitis optica have considered the syndrome a specific disease. Clinically, the unusual combination of sudden blindness and crippling paraplegia has made this syndrome appear unique. Pathologically, the severity of the lesions both in the optic nerves and in the spinal cord has contributed to the apparent unicity of the disease. It is significant that the men who have studied the disease extensively have favored the idea of specificity; Goulden,[10] Beck,[12] McAlpine,[14] Walsh,[17] Balser,[18] Hassin [20] and Michaux [30] have all expressed that opinion. Nevertheless,

160. Denny-Brown, D., and Brenner, C.: Lesion in Peripheral Nerve Resulting from Compression by Spring Clip, Arch. Neurol. & Psychiat. **52**:1-19 (July) 1944.

the proof that neuromyelitis optica is a specific disease, namely, the demonstration of the causative agent, is lacking.

The similarity between neuromyelitis optica and multiple sclerosis was noted long ago; Dreschfeld[111] in 1894 first called attention to the pathologic likenesses. Symonds[161] was first to insist on the identity of the two conditions; discussing Beck's case in 1927, he stated that it was actually a rapidly progressive case of multiple sclerosis and pathologically identical with a case of multiple sclerosis in which he had done an autopsy a few years before.[162] According to Symonds, the apparent differences between the two conditions are merely variations in acuteness and intensity. This view has become increasingly popular, especially in the United States, where the theory has particularly been espoused by Putnam and Ferraro. These authors and their colleagues have come to the conclusion that all the demyelinating diseases are fundamentally uniform in their basic pathology. They attribute the confusing clinical diversity of these diseases to differences in distribution and severity of the pathologic lesions and to differences in age, resistance and constitution of the patients. In regard to classification, they maintain that only secondary and unimportant features have been used as criteria for splitting the demyelinating diseases into a multitude of clinical and pathologic divisions and subdivisions.

The essential problem in the differential diagnosis of neuromyelitis optica today, then, is the differentiation (if any) of this syndrome from the other demyelinating diseases: (1) multiple sclerosis, (2) the diffuse scleroses and (3) the acute disseminated encephalomyelitides. Until the etiologic agent in these diseases is discovered, clinical and pathologic characteristics constitute the only available basis for discussion.

Multiple Sclerosis.—Although the school of Putnam and Ferraro consider neuromyelitis optica and multiple sclerosis as more or less identical, many other investigators have not agreed and have described a number of differentiating features. The following points of differential diagnosis have been accumulated from the literature, and do not necessarily represent my opinion.

Clinical Differences: 1. Course of the Disease: Neuromyelitis optica is an acute, self-limiting disease, ending in death or in recovery in a relatively short period, whereas multiple sclerosis is a chronic, relapsing disease with a slow downhill course. Variability in its course is a characteristic of multiple sclerosis, while the course of neuromyelitis optica is comparatively uniform. Remissions are very common in the former but relatively uncommon in the latter.

161. Symonds, C. P., in discussion on Beck,[12] 703.

162. Symonds, C. P.: The Pathological Anatomy of Disseminated Sclerosis, Brain **47**:36-56, 1924.

2. Loss of Vision: Sudden binocular loss of vision is almost pathognomonic of neuromyelitis optica but rare in multiple sclerosis (Brain,[168] McIntyre and McIntyre[164]). The severity of the visual loss in neuromyelitis optica is usually greater than that in multiple sclerosis, in which it is unusual for even one eye to become totally blind and bilateral total blindness is almost unknown.

3. Occurrence in Children: It is almost universally accepted that multiple sclerosis does not occur before puberty (Garrod and associates[165]) whereas neuromyelitis optica is frequently reported in children. Wechsler[166] and Brain[167] suggested that the few published reports of multiple sclerosis in children represent mistaken diagnoses.

4. Nystagmus: This is a most common occurrence in multiple sclerosis (70 per cent of cases, Brain[167]), but all authors agree that it is rare or nonexistent in neuromyelitis optica. The absence of nystagmus was stated to be one of the main differentiating points by Michaux.[30]

5. Collodial Gold Curve: It is generally accepted that there is a characteristic colloidal gold curve (Merritt[168]) of the spinal fluid in multiple sclerosis, whereas the findings are normal, or at least noninformative, in cases of neuromyelitis optica.

6. Other Clinical Differences: Pain is uncommon in multiple sclerosis while Balser[18] and McAlpine[25] found pain in the extremities and back a common mode of onset in neuromyelitis optica. Balser and others called attention to the fact that mental disturbances, such as euphoria, are frequent in multiple sclerosis but rare in neuromyelitis optica. Walsh[17] and McAlpine[25] cited the relative absence of palsies of the extraocular muscles in the latter disease, as compared with their occurrence in disseminated sclerosis. Hassin[169] mentioned that the tendon reflexes are almost always exaggerated in multiple sclerosis, but that they are diminished or lost, after an initial period of hyperactivity, in neuromyelitis optica.

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163. Brain, W. R.: Critical Review: Disseminated Sclerosis, Quart. J. Med. **23**:343-391, 1930.

164. McIntyre, H. D., and McIntyre, A. P.: Prognosis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **50**:431-438 (Oct.) 1943.

165. Garrod, A. E.; Batten, F. E.; Thursfield, H., and Paterson, D.: Diseases of Children, New York, William Wood & Company, 1929, pp. 753-754.

166. Wechsler, I. S.: A Textbook of Clinical Neurology, Philadelphia, W. B. Saunders Company, 1931, pp. 548.

167. Brain, R.: Diseases of the Nervous System, London, Oxford University Press, 1947, p. 503.

168. Merritt, H. H.: The Cerebro-Spinal Fluid in Multiple Sclerosis, Brain **57**:56-68, 1934.

169. Hassin, G. B., in discussion on Putnam and Forster.[27]

Pathologic Differences: 1. Distribution of the Lesions: The whole central nervous system is commonly involved in the pathologic changes of multiple sclerosis, whereas in neuromyelitis optica the brain and the brain stem are not usually affected. The optic pathways are always involved in the latter disease (by definition), but are never so constantly affected in multiple sclerosis. The cerebellum is commonly involved in multiple sclerosis but seldom in neuromyelitis optica.

2. Involvement of the Gray Matter: Multiple sclerosis is practically limited to the white matter of the nervous system, but the gray substance is impartially involved in the lesions of neuromyelitis optica. Further, Hassin [170] added that when the gray matter is involved in multiple sclerosis the changes are slight and the ganglion cells spared, in contradistinction to the death of nerve cells seen in neuromyelitis optica.

3. Destruction of Axis-Cylinders: Many authors have expressed the opinion that the active phase of multiple sclerosis is restricted to the destruction of myelin sheaths and that the process ends when this is completed. On the other hand, the disintegration of axis-cylinders is a characteristic feature of neuromyelitis optica.

4. Cellular Infiltration: Those who favor the specificity of neuromyelitis optica state that polymorphonuclear leukocytes (early), lymphocytes and plasma cells are noted in great numbers in that disease but that collections of these cells are rare in multiple sclerosis. They also state that perivascular round cell infiltration is widespread throughout the nervous system in neuromyelitis optica, irrespective of the foci of necrosis, and that this is not a feature in multiple sclerosis.

5. Cavitation: Rarefaction of tissue, progressing to gross cavitation, is frequently reported in cases of neuromyelitis optica but never in cases of multiple sclerosis. Lowenberg [171] stated that the abundant proliferation of fibrous glia in multiple sclerosis insures a scar (plaque), so that cavity formation cannot occur.

6. Gliosis: This is seldom seen with neuromyelitis optica, but it is the *sine qua non* of multiple sclerosis. Hassin [170] explained that the plaques of multiple sclerosis are composed of fibrillary astrocytes, which are rarely seen in the other disease.

7. Size of Lesions: In neuromyelitis optica the lesions may be very large (one lesion may involve several segments of the spinal cord—fourteen continuous segments in Beck's case), whereas the plaques of multiple sclerosis are small and circumscribed.

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170. Hassin, G. B.: Histopathology of the Peripheral and Central Nervous System, New York, Paul B. Hoeber, Inc., 1940, pp. 106-117.

171. Lowenberg, K., in discussion on Putnam and Forster,[27] pp. 22-23.

8. Other Pathologic Differences: McAlpine [25] stressed the degree of severity as a differentiating factor, stating that the acute necrosis of neuromyelitis optica is not observed with multiple sclerosis. Other authors have said that the acute process in neuromyelitis optica involves whole bundles of nerve fibers at one time, whereas in multiple sclerosis this wholesale destruction does not occur; instead, single nerve fibers undergo successive degeneration. The proliferation of capillaries seen in neuromyelitis optica was given as a differential point by Balser [18] and McAlpine,[25] who had not seen this proliferation in multiple sclerosis.

The Diffuse Scleroses.—In 1912 Schilder [172] described a malady of children and young adults characterized by sudden loss of vision, spastic paralyses, mental deterioration and death in a few months. Pathologically, he observed symmetric diffuse demyelination of the centrum ovale. He called this syndrome "encephalitis periaxialis diffusa," but it has become better known as Schilder's disease. Bouman [173] collected 24 cases of this syndrome in 1924 and published the first survey of the meager literature. She found Schilder's disease characterized histologically by demyelination, destruction of axons, proliferation of astrocytes, gliosis and microglial proliferation. Clinically, the common signs were mental deterioration, spastic paralyses, loss of vision, extraocular muscle palsies, facial palsy and dysarthria. Collier and Greenfield [174] stressed the importance of cerebral blindness in this disease, calling it the chief early sign. Stewart and associates [175] found that central deafness may be the first symptom. In 1924 Globus and Strauss [176] discarded Schilder's restriction of the pathologic alterations to the brain proper when they found lesions throughout the cerebrospinal axis. Brock and associates [177] emphasized the importance of the ocular disturbances; they found loss of vision, field defects, optic neuritis, abnormal pupillary reactions, muscle palsies, nystagmus and

172. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose: Ueber Encephalitis periaxialis diffusa, Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:1-60, 1912.

173. Bouman, L.: Encephalitis Periaxialis Diffusa, Brain **47**:453-488, 1924.

174. Collier, J., and Greenfield, J. G.: The Encephalitis Periaxialis Diffusa of Schilder: A Clinical and Pathological Study, with an Account of Two Cases, One of Which Was Diagnosed During Life, Brain **47**:489-519, 1924.

175. Stewart, T. G.: Greenfield, J. G., and Blandy, M. A.: Encephalitis Peri-Axialis Diffusa: Report of Three Cases with Pathological Examination, Brain **50**:1-29, 1927.

176. Globus, J. H., and Strauss, I.: Progressive Degenerative Subcortical Encephalopathy: Schilder's Disease, Arch. Neurol. & Psychiat. **20**:1190-1228 (Dec.) 1928.

177. Brock, S.; Carroll, P. M., and Stevenson, L.: Encephalitis Periaxialis Diffusa of Schilder: Report of a Case, Arch. Neurol. & Psychiat. **15**:297-308 (March) 1926.

paralyses of gaze. Gasul [178] collected 71 cases from the literature and stated that some loss of vision, with normal pupils, occurred in almost every case.

A number of other demyelinated conditions have been described which differ from Schilder's disease only in name and some minor clinical or pathologic details. Pelizaeus [179] published the clinical features and Merzbacher [180] the pathologic description of what is known as Pelizaeus-Merzbacher disease; this condition also occurs in children and differs from Schilder's disease only in its chronicity and a later onset of blindness. Krabbe [181] reported a variation of diffuse sclerosis in infants, distinctive only in a familial tendency. Scholz [182] described the juvenile form of the cerebral scleroses, differentiated by a later onset of symptoms (at 8 to 10 years of age). Baló [106] announced the discovery of a new type, characterized by destruction of the cerebral white matter in concentric layers. Indicative of the confusion in this neuro-ophthalmologic jungle is the predicament of Baker and Gerber,[183] who reported a case that was pathologically either of Schilder's or of Krabbe's disease but the patient was too young for Schilder's disease and there was no familial tendency to connect it with Krabbe's type.

Differential Diagnosis.—Clinically, many differences have been cited between this group of syndromes and neuromyelitis optica. Most reports have stressed the normal pupil of cerebral blindness (pathognomonic of the diffuse scleroses) as compared with the dilated, immobile pupil of neuromyelitis optica. The mental deterioration, cortical deafness and other cerebral symptoms of the diffuse scleroses are not usually found in neuromyelitis optica. The age incidence and the familial tendency in the scleroses group are also used to differentiate the two conditions. Pathologically, the diffuse scleroses are

178. Gasul, B. M.: Schilder's Disease (Encephalitis Periaxialis Diffusa): A Review of the Literature and Report of a Case, Am. J. Dis. Child. **39**:595-609 (March) 1930.

179. Pelizaeus, F.: Ueber eine eigenthümliche Form spastischer Lähmung mit Cerebralerscheinungen auf hereditärer Grundlage (multiple Sklerose), Arch. f. Psychiat. **16**:698-710, 1885.

180. Merzbacher, L.: Eine eigenartige familiär-hereditäre Erkrankungsform: Aplasia axialis extracorticalis congenita, Ztschr. f. d. ges. Neurol. u. Psychiat. **3**:1-138, 1910.

181. Krabbe, K.: A New Familial, Infantile Form of Diffuse Brain-Sclerosis, Brain **39**:74-114, 1916.

182. Scholz, W.: Klinische, pathologische-anatomische und erbbiologische Untersuchungen bei familiärer, diffuser Hirnsklerose im Kindesalter: Ein Beitrag zur Lehre von den Heredodegenerationen, Ztschr. f. d. ges. Neurol. u. Psychiat. **99**:651-682, 1925.

183. Baker, A. B., and Gerber, L. S.: Cerebral Sclerosis, Am. J. Dis. Child. **59**:522-534 (March) 1940.

apparently identical with neuromyelitis optica in microscopic section. The only significant difference lies in the distribution of the lesions, the pathologic changes in the scleroses being mainly cerebral while the lesions of neuromyelitis optica are infrequently observed in the brain.

The Acute Disseminated Encephalomyelitides.—Postvaccinal encephalomyelitis has been known ever since jennerian prophylaxis became popular; but, for some unknown reason, a definite increase in the incidence has been noted in the past twenty-five years. Most cases occur, obviously in children, and about one-half the cases are fatal. Cerebral symptoms are prominent, and flaccid paralyses with incontinence are the principal signs of involvement of the spinal cord. The ocular complications were summarized by Herrenschwand [184]; he described (1) optic neuritis with transient blindness, followed by secondary optic nerve atrophy; (2) mild primary optic nerve atrophy; (3) transient paralyses of the oculomotor nerve, and (4) bilateral palsies of the abducens nerve. The pathologic features (Turnbull and McIntosh [185]) consist of congestion of the brain and spinal cord, destruction of the gray matter, perivascular demyelination and lymphocytic infiltration. Perdrau [186] found the lesions similar to those of multiple sclerosis. An encephalomyelitis also follows smallpox (Wilson and Ford,[187] Marsden and Hurst [188]) that is indistinguishable from that following vaccination. Encephalitis following Pasteur prophylaxis against rabies has not infrequently been reported; the lesions are histologically similar to those of the other encephalomyelitides. Ocular lesions are not prominent.

Postmeasles encephalomyelitis has been known for one hundred years; it occurs in about 0.5 per cent of cases of measles, coming on about five days after the onset of the exanthem. A wide variety of symptoms are encountered, according to the location of the lesions. A number of pathologic patterns have been described by Ford [189]: a meningismus-like type, multiple focal lesions, single focal lesions, a cerebellar type, a spinal cord type and optic neuritis alone. This

184. Herrenschwand, F.: Zur Beteiligung des Sehnerven bei Encephalomyelitis Postvaccination, Klin. Monatsbl. f. Augenh. **102**:815-823, 1939.

185. Turnbull, H. M., and McIntosh, J.: Encephalomyelitis Following Vaccination, Brit. J. Exper. Path. **7**:191-222, 1926.

186. Perdrau, J. R.: The Histology of Post-Vaccinal Encephalitis, J. Path. & Bact. **31**:17-32, 1928.

187. Wilson, R. E., and Ford, F. R.: Nervous Complications of Variola, Vaccinia, and Varicella, Bull. Johns Hopkins Hosp. **40**:337-353, 1927.

188. Marsden, J. P., and Hurst, E. W.: Acute Perivascular Myelinoclasis ("Acute Disseminated Encephalomyelitis") in Smallpox, Brain **55**:181-225, 1932.

189. Ford, F. R.: The Nervous Complications of Measles, with a Summary of the Literature and Publication of Twelve Additional Case Reports, Bull. Johns Hopkins Hosp. **43**:140-184, 1928.

variability explains the diverse ocular findings, i. e., papilledema, optic neuritis, dilated pupils, central scotomas, homonymous hemianopsias, visual hallucinations and extraocular muscle palsies. Measles encephalitis sometimes closely resembles neuromyelitis optica. Encephalomyelitis following rubella has also been described (Margolis, Wilson and Top[190]); diplopia, nystagmus and sluggish pupillary reactions constitute the reported ocular findings.

A more benign form of encephalomyelitis is seen after chickenpox (Walsh[68]), similar in every way to the postmeasles type except in severity. Ophthalmologically, optic neuritis, with visual loss, optic nerve atrophy, ptosis, extraocular muscle palsies and nystagmus, has been reported. There is a high rate of recovery (about 90 per cent), both from the general and from the ophthalmologic point of view. Ferraro[191] reported a similar encephalomyelitis following scarlet fever. A severe encephalomyelitis occurs in conjunction with mumps; this type is usually associated with meningitis and is not likely to be confused with the demyelinating diseases. Scheinker,[192] however, reported a case of mumps encephalomyelitis similar in all respects to the postmeasles and postvaccination types.

Differential Diagnosis.—Clinically, there is little in common between these encephalomyelitides and neuromyelitis optica. The history of the preceding infection or vaccination usually points to the diagnosis in the former conditions, which occur in great preponderance in children. The prominence of the cerebral signs and symptoms and the frequent involvement of the cerebellum in the disseminated encephalomyelitides constitute important clinical differences. The only similarity of any consequence is the involvement of the optic pathway that is common to both neuromyelitis optica and the encephalomyelitides. Pathologically, the latter conditions differ from neuromyelitis optica in that (1) they exhibit small, discrete lesions that do not tend to coalesce into large foci, (2) they commonly show gliosis and (3) their lesions reveal a decided inflammatory nature.

Comment.—It is obvious that the demyelinating diseases exhibit many similarities, and especially is this true of multiple sclerosis and neuromyelitis optica. It must be admitted that in some cases Devic's disease is indistinguishable clinically from multiple sclerosis. Many

190. Margolis, F. J.; Wilson, J. L., and Top, F. H.: Post-Rubella Encephalomyelitis: Report of Cases in Detroit and Review of Literature, J. Pediat. **23**:158-165, 1943.

191. Ferraro, A.: Allergic Brain Changes in Post-Scarlatinal Encephalitis, J. Neuropath. & Exper. Neurol. **3**:239-254, 1944.

192. Scheinker, I. M.: Disseminated Encephalomyelitis and Its Relation to Multiple Sclerosis, J. Neuropath. & Exper. Neurol. **2**:418-419, 1943.

of the differences in the clinical picture (differences in course, visual loss and presence or absence of cerebral symptoms) can be plausibly explained as the result of variation in the severity of the process, in the location of lesions and in the reaction of the patient. Other differences are difficult to explain. The fact that nystagmus is seen in almost all cases of advanced multiple sclerosis, and yet is rare in neuromyelitis optica, is one such problem. The common occurrence of optic neuromyelitis in children, whereas multiple sclerosis is not seen before puberty, is another factor not easily elucidated.

In the same manner, most of the variations in the pathology may well be due to differences in the location and severity of lesions. The involvement of the gray matter, the destruction of axis-cylinders, the more abundant cellular exudate and the greater size of the lesions in neuromyelitis optica, as compared with multiple sclerosis, might be attributed to the factors mentioned. Again, however, there are dissimilarities that are not easily explained. One of these is the occurrence of cavitation in neuromyelitis optica and the lack of it in multiple sclerosis, even in the so-called acute multiple sclerosis. Another is the universal occurrence of gliosis (plaques) in multiple sclerosis and the paucity of gliosis (and total lack of plaques) in neuromyelitis optica, even in the more chronic cases.

One must remember that neuromyelitis optica is usually seen at autopsy in the early, acute stage, while multiple sclerosis is seldom seen except in a late stage of the chronic type in old patients who die of some other cause. This suggests an interesting objective point of differentiation, namely, that patients die of neuromyelitis optica but not of multiple sclerosis. This factor offers ground for interesting speculation. So much has been written about the pathology of multiple sclerosis, and yet there is a dearth of material classified under that diagnosis in our pathologic laboratories. In the pathologic collection of the Presbyterian Hospital (representing over 15,000 autopsies, performed in the past thirty years), there are no cases in which death was due to multiple sclerosis. (There are 3 cases listed under that diagnosis, but in each instance the diagnosis was secondary, the patient having old multiple sclerosis but dying of some other cause). The rarity of pathologic material is not mentioned in the voluminous literature on multiple sclerosis, and yet many writers discuss the pathology of active multiple sclerosis with assurance. These facts tend to weaken some of the positive statements frequently made regarding the similarity of the pathology of this disease to that of neuromyelitis optica.

Moreover, if one accedes pathologic similarity in these diseases, the problem is still not solved. The crux of the matter then becomes whether or not clinical and histologic similarity is sufficient basis for hypothesizing a common etiology, and so identity. It must be admitted

that it is not. Clinical likenesses are notoriously fallible for purposes of such an assumption. Pathology as the basis for etiologic diagnosis has already been discussed under etiology. To repeat, there appears to be no logical reason for assuming a common cause because of similar, or even identical, pathology.

With regard to the diffuse scleroses, there is no substantial reason for so many different forms, the differentiation relying on such insecure factors as age at onset, duration of course and questionable familial tendencies. Their main bond with neuromyelitis optica is the similarity of the histologic picture, and, for the reasons already given, this does not prove a common identity. The same comment pertains to the acute encephalomyelitides. In fact, the initiation of this pathologic picture by so many different stimuli in the encephalomyelitides might well be offered as an argument against the unity of the demyelinating diseases.

SUMMARY

In view of the new theory of the common identity of the demyelinating diseases, neuromyelitis optica assumes a new importance. It has a much greater mortality rate than multiple sclerosis and therefore affords more material for pathologic study.

The important early contributions to the study of neuromyelitis optica are summarized, and the literature since 1927 is briefly discussed.

Five cases of neuromyelitis optica have been diagnosed in the Columbia-Presbyterian Medical Center in the past twenty years. The clinical records and the pathologic findings of these cases are presented.

Twenty cases of neuromyelitis optica, substantiated by postmortem examination, were studied in an effort to establish the common clinical features. This survey showed that this disease occurs commonly between the ages of 30 and 50 years, more often in females and is not limited to persons of the white race. The initial symptoms are referable to the visual system in one-half the cases and to the spinal cord in the rest. Severe binocular loss of vision is characteristic. In most cases there was optic nerve atrophy of some kind, associated with a central scotoma or complete loss of the visual field. The rapidly ascending nature of the myelitis is the only characteristic neurologic finding. Remissions occur in about one-half the cases. The patient frequently dies in the first three months of his illness, and in the fatal cases the survival is seldom over two years. There are no characteristic laboratory findings and no efficacious therapy.

The pathologic features in these 20 cases were also surveyed. It was found that the lesions of neuromyelitis optica commonly occur in the optic pathway, spinal cord and brain stem, and occasionally in the cerebrum. Histologically, the disease is characterized by demyelination

of nerves, destruction of axis-cylinders, mild astrocytosis, pronounced microglial proliferation, perivascular infiltration of white blood cells, proliferation of capillaries and, sometimes, gross cavitation.

A composite, chronologic description of the microscopic process in neuromyelitis optica, with illustrative photomicrographs, is presented.

The five principal etiologic theories of the demyelinating diseases are (1) the infectious theory, (2) the toxic theory, (3) the enzyme theory, (4) the theory of vascular obstruction and (5) the allergic theory. None of these theories has been substantiated. The evidence for and against each is weighed.

It is suggested that too much emphasis has been placed on the most obvious finding in these diseases, namely, demyelination of nerve fibers. Demyelination appears to be one of the first reactions of nerve tissue to trauma, and a multitude of injuries may cause this loss of myelin. There is no evidence, therefore, that demyelination is of any particular etiologic or pathologic significance.

The hypothesis of the common etiology of the demyelinating disease group rests mainly on the demonstration of a similar pathologic process. It is suggested, however, that the demonstration of similar, or even identical, pathologic changes does not prove the existence of a common etiologic agent. It would appear more logical to attempt to fulfil Koch's postulates in the conventional manner.

The case reports in this paper are presented with the permission of Dr. Edwin G. Zabriskie, acting director of the Neurological Institute of New York.

The pathologic material was made available to me by Dr. Harry Pratt Smith, director of pathology, Presbyterian Hospital.

Dr. Abner Wolf and Dr. David Cowen rendered invaluable assistance in the interpretation of the pathologic picture.

Dr. Frank P. Carroll assisted in the interpretation of the ophthalmologic findings.

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News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

National Society for the Prevention of Blindness.—The National Society for the Prevention of Blindness will hold a five day conference in conjunction with the interim session of the Pan-American Association of Ophthalmology, March 26 to 30, 1950, at the Floridian Hotel, Miami Beach, Fla. The theme of the meeting will be "The Americas Unite to Save Sight"; and among the subjects to be discussed are current blindness prevention programs in countries of the Western Hemisphere, trachoma, industrial ophthalmology, ophthalmologic problems of school children and medical and social management of the glaucomas.

Persons directly or indirectly concerned with the health and safety of the eyes will find this conference of interest. Details concerning the program may be obtained by writing directly to the National Society for the Prevention of Blindness, 1790 Broadway, New York 19.

Reservations should be made in the near future with the Floridian Hotel, 540 West Avenue, Miami Beach, Fla.

Annual Spring Graduate Course of the Gill Memorial Eye, Ear and Throat Hospital.—The Twenty-Third Annual Spring Graduate Course of the Gill Memorial Eye, Ear and Throat Hospital will be held in Roanoke, Va., April 3 to 8, 1950. The guest faculty is as follows:

Dr. F. W. Stocker, Durham, N. C.; Dr. Conrad Berens, New York; Dr. Fred Wilson, Chicago; Dr. C. W. Mayo, Rochester, Minn.; Dr. Edmund B. Spaeth, Philadelphia; Dr. Arthur J. Bedell, Albany, N. Y.; Dr. James J. Regan, Boston; Dr. W. Gayle Crutchfield, Charlottesville, Va.; Dr. Stuart Cullen, Iowa City; Dr. Richard G. Scobee, St. Louis; Dr. Daniel S. Cunning, New York; Dr. Alson E. Braley, New York; Dr. Karl M. Houser, Philadelphia; Dr. Hugo L. Bair, Rochester, Minn.; Dr. Gabriel Tucker, Philadelphia; Dr. Edward M. Walzl, Baltimore; Sir Alexander Fleming, London, England; Dr. J. Barrett Brown, St. Louis; Dr. Walter B. Hoover, Boston; Dr. Oscar C. Hansen-Pruss, Durham, N. C.

CORRECTION

In the article by Dr. K. W. Ascher entitled "Aqueous Veins and Their Significance for Pathogenesis of Glaucoma," published in the July issue of the ARCHIVES, line 9 on page 67 should read, "eye [7] and in eyes of experimental animals [8]; they can be photographed . . ."

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

SJÖGREN SYNDROME. C. ESPILDORA LUQUE, J. MOSSER and A. GORMAZ, Arch. Soc. oftal. hispano-am. **8:** 333 (April) 1948.

The filamentous keratitis associated with diminished lacrimal secretion, mentioned by Wagenmann and Leber at the end of the last century, was the first symptom of the Sjögren syndrome to be described. In 1919 Fuchs related his observation of a case and suggested the possibility of the association of this symptom with a systemic condition. This was a further step in the description of the syndrome in question. After this many authorities reported similar cases, until Sjögren made a full study of the condition and described all the symptoms which constitute the syndrome now bearing his name.

The authors are of the opinion that the filamentous keratitis primarily described by Wagenmann and Leber is not of a type associated with this syndrome. The type occurring in this pathologic entity is microscopic. The filaments present are in the form of fine, white threads, lying loose on the cornea and floating in a grumous, sticky fluid, which forms a whitish foam at both canthi.

The keratoconjunctivitis sicca described by Duke-Elder is the one which integrates the Sjögren syndrome, being accompanied with dryness of the conjunctiva and of the mucous membrane of the mouth, pharynx and larynx, hypertrophy of the parotid gland, arthritis, and other changes.

The syndrome may or may not be initiated by the ocular symptom. In 9 cases reported by the authors the ocular manifestations began many years after onset of the arthritis. In other cases the condition was initiated by an acute inflammation of the salivary glands or by dryness of the mouth.

A detailed discussion of the etiology, pathogenesis, symptomatology, differential diagnosis and treatment of the syndrome is made. Nine new cases are reported.

The article is illustrated.

H. F. CARRASQUILLO.

SUBCONJUNCTIVAL INJECTIONS OF BLOOD IN MANAGEMENT OF DISEASES OF THE CORNEA. Z. PALTZEVA, Vestnik oftal. **25:** 34, 1946.

Paltzeva used diluted blood in the treatment of 33 patients with purulent corneal ulcers and of 5 patients with herpetic keratitis. The technic was as follows: To 0.45 cc. of distilled water in the syringe is added 3 drops of blood taken from the patient's finger; the mixture is shaken until it becomes transparent, and 0.2 of it is injected subconjunctivally near the limbus.

The injections were given every other day for a total of two to eight injections. Trauma was the etiologic factor in the corneal ulcer in

20 cases. Bacteriologic examination showed the presence of the white staphylococcus in 14 cases, the pneumococcus in 7 cases and the streptococcus in 3 cases. In 20 cases epithelization of the ulcer occurred after two to four injections, and in the others from five to eight injections were required for complete epithelization of the cornea and absorption of the hypopyon. The blood count showed an increase of the red and the white blood cells.

Paltzeva believes that it is worth while to try this simple method, as no complications were observed, the subjective symptoms were relieved and epithelization and absorption of hypopyon were speeded up. Case histories and a table illustrate the improvement of vision.

O. SITCHEVSKA.

Glaucoma

PROVOCATIVE TESTS IN THE DIAGNOSIS OF THE GLAUCOMAS. H. S. SUGAR, Am. J. Ophth. **31:** 1193 (Oct.) 1948.

Sugar concludes that the combined water and pressor–congestion test gives higher responses in cases of glaucoma than either of these tests alone. In the combined test a rise of over 10 mm., or to over 38 mm., may be considered positive. No provocative test is of greater diagnostic value than routine and repeated tonometry in diagnosis of glaucoma in patients over 40 years of age.

W. S. REESE.

GONIOSCOPIC FINDINGS IN PRIMARY GLAUCOMA. J. FRANCOIS, Ann. d'ocul. **181:** 399 (July) 1948.

The author discusses the various changes in the angle of the anterior chamber that are said to occur in glaucoma. Barkan's classification of wide and narrow angle glaucoma is referred to. The data on 32 cases of glaucoma are presented. From these, the author concludes that in chronic simple glaucoma there are no pathognomonic signs in the angle. One may find certain abnormalities, but they are also seen in eyes that do not have increased tension. In congestive glaucoma the angle is very narrow when the tension is raised. After the congestive phase numerous synechias are found; these are more numerous if the tension has been raised for some time. In unilateral chronic simple glaucoma the angles of the eyes appear the same. In congestive glaucoma the angle is always narrower in the diseased eye.

P. R. MCDONALD.

BASAL METABOLISM IN GLAUCOMA. A. KOLENKO, Vestnik oftal. **25:** 45, 1946.

The basal metabolism was measured in 100 patients with glaucoma; of these 71 patient had primary glaucoma, in various stages, and 29 had secondary glaucoma. Lowering of the basal metabolic rate was observed in some patients with primary glaucoma. There was no increase of the basal metabolism in the patients with secondary glaucoma. Further investigation will follow.

O. SITCHEVSKA.

Experimental Pathology

EXPERIMENTAL DIABETIC CATARACT IN RATS. F. E. D. CRAMER and V. G. FOGLIA, Arch. de oftal. de Buenos Aires **13:** 101 (April-June) 1948.

Experiments were conducted on depancreatized rats to observe the development of cataract. The removal of 95 per cent of the pancreas by the technic of one of the authors (Foglia) produced diabetes within six months in 92 per cent of the male rats and in 28 per cent of the female rats. The rats lived seven months or more, allowing plenty of time for study of the formation of lenticular opacities. The diabetic cataract appeared in these rats at least seventy days after 95 per cent of the pancreas was removed and two hundred days after only 80 per cent of the organ was excised. Once the first changes made their appearance, the alterations continued until the lens became totally opaque.

The progress in the development of the opacities was in relation to the intensity of the diabetes present in the animal. In no case did retrograde changes take place after the cataract was formed. The lens showed pronounced histologic changes, as well as chemical modifications. The article is illustrated.

H. F. CARRASQUILLO.

General Diseases

TUBERCULOSIS OF THE CHOROID IN A CASE OF MILIARY TUBERCULOSIS TREATED WITH STREPTOMYCIN. J. P. HALBERG, Ann. d'ocul. **181:** 485 (Aug.) 1948.

The authors report the case of a 16 year old boy with miliary tuberculosis who showed evidence of miliary tubercles in the choroid of both eyes. He received 247.5 Gm. of streptomycin over a period of four months, with no toxic manifestations. The pulmonary tuberculosis receded rapidly, and the choroidal lesions showed progressive cicatrization.

P. R. MCDONALD.

TOXOPLASMOSIS. C. D. BINKHORST, Ophthalmologica **115:** 65 (Feb.) 1948.

The clinical signs most commonly encountered in cases of toxoplasmosis in infants are chorioretinitis, cerebral calcifications, encephalomyelitis with hydrocephalus, fits, vomiting, fever, paresis, xanthochromia and an increase of albumin and cells in the spinal fluid. In adults the most frequent findings are pneumonia, fever, exanthems and gastroenteritis. In most cases the chorioretinitis is circumscribed, bilateral and central. The condition is frequently acquired in utero and is then usually fatal. Diagnosis is based on biopsy observations, the complement fixation reaction, changes in the spinal fluid and the appearance of toxoplasmas in the mouse brain after intracerebral injection of infected spinal fluid.

This report is the first in the European literature of a case in which the diagnosis was made during life by the demonstration of toxoplasma-like parasites in the mouse brain after the injection of spinal fluid. The article is illustrated.

H. P. KIRBER.

CHANGES IN THE EYE, ESPECIALLY IN THE FUNDUS, ACCOMPANYING TUBERCULOSIS OF THE SKIN. L. NÉMETH, Ophthalmologica **115:** 167 (March) 1948.

The author includes under the heading "tuberculoderma" lupus, scrofuloderma, lupus erythematosus, erythema induratum (Bazin's disease) and sarcoidosis (Boeck's sarcoid). Of 36 cases of tuberculoderma he found changes in the eyegrounds in 8. In 6 of these cases an old choroiditis existed, and in 2, papillitis, retinitis and small tubercles. The acute exudative, as well as the chronic proliferative, type of tuberculosis involving the choroid, retina and optic nerve can be found in patients with tuberculosis of the skin. H. P. KIRBER.

Lids

SOME METHODS OF LID REPAIR AND RECONSTRUCTION. S. A. FOX, Am. J. Ophth. **31:** 1441 (Nov.) 1948.

Fox describes an operative method of constructing an inferior cul-de-sac which is essentially the old method of Snellen sutures.

W. S. REESE.

TREATMENT OF HORDEOLUM WITH INTRAPALPEBRAL INJECTION OF PENICILLIN. M. T. ROSAS COSTA, An. Argent. de oftal. **8:** 13 (Jan.-March) 1947.

The author believes that the use of penicillin is the most efficacious of all methods of treatment of hordeolum. He uses it locally in perifocal injection. He injects 50,000 Oxford units dissolved in 1 cc. of a 2 per cent solution of procaine hydrochloride. The hordeolum is cured in from twelve to twenty-four hours. H. F. CARRASQUILLO.

Neurology

INVOLVEMENT OF THE OPTIC CHIASM IN VON RECKLINGHAUSEN'S DISEASE (NEUROFIBROMATOSIS). P. E. TIKHOMIROV, Vestnik oftal. **26:** 25, 1947.

Involvement of the visual apparatus in neurofibromatosis occurs in the lids in the form of plexiform neurofibroma, or fibroma molluscum; in the conjunctiva, sclera, cornea, iris, choroid and ciliary body, nodules are observed occasionally. Tumors in the retina, the optic nerve and the optic chiasm may also be present. Hydrophthalmos, glaucoma, optic nerve atrophy, defects of the orbital walls and enlargement of the sella turcica may be secondary to general neurofibromatosis.

Tikhomirov reports a case of neurofibromatosis with the rare occurrence of tumor in the chiasm. A woman aged 35 was hospitalized because of blindness in the left eye and impairment of vision in the right eye. There was a mature cataract in the left eye with faulty light projection. In the left eye, vision was reduced to 0.5, and there were atrophy of the optic nerve and concentric constriction of the visual fields. The roentgenogram showed destruction of the sella turcica and

the upper medial wall of the optic canal with its enlargement. The patient had multiple pigmented neurofibromas on the neck, the back and the extremities.

Thus, the descending optic nerve atrophy of both eyes and the destruction of the posterior wall of the sella turcica indicated the presence of an intrasellar tumor, which, in view of the general neurofibromatosis, could be classified as of the neurinoma or the schwannoma type.

O. SITCHEVSKA.

Ocular Muscles

ANALYSIS OF OCULAR MOTOR ANOMALIES. W. C. OWENS, Am. J. Ophth. **31:** 1297 (Oct.) 1948.

Owens describes the motility clinic at Johns Hopkins Hospital and emphasizes the necessity of a standardized method of analysis of oculomotor anomalies.

W. S. REESE.

FACTORS IN THE SURGICAL TREATMENT OF VERTICAL DEVIATIONS. J. H. DUNNINGTON, Am. J. Ophth. **31:** 1404 (Nov.) 1948.

Dunnington points out that recent knowledge has shown that most deviations of vertically acting muscles are of paralytic origin. Selection of the proper operative procedure in a given case of paralysis depends not only on the amount of deviation present in the various directions of gaze but also on the eye used for fixation. The surgical treatment of each type of paralysis is reviewed, and the importance of the "fixing eye" in the selection of the proper surgical approach is pointed out.

W. S. REESE.

POSTOPERATIVE HYPERTROPIA. R. G. SCOBEE, Am. J. Ophth. **31:** 1437 (Nov.) 1948.

In this interesting article, Scobee states that there is no such thing as unintentional postoperative hypertropia. It is really preoperative and simply requires careful diagnostic study for its recognition.

W. S. REESE.

Operations

TECHNIC OF FINISHING THE KERATOTOMY AND MAINTAINING THE SPHINCTER OF THE IRIS WHEN THE KNIFE ENGAGES THE IRIS. J. SÉDAN and S. SÉDAN-BAUBY, Ann. d'ocul. **181:** 414 (July) 1948.

The authors state that in cataract extractions a keratome incision enlarged with scissors is popular on the Continent and in the United States. There are many surgeons, however, who prefer to use a Graefe knife. One of the disadvantages of using a Graefe knife is that the iris may be caught on the knife, and if the corneal section is completed a ragged iridectomy is obtained. The authors believe that preservation of the sphincter of the iris is important and that every possible means should be taken to preserve its integrity. The literature on the avoidance and handling of this complication is reviewed.

The authors present their methods of handling this complication. Their method of choice is to withdraw the Graefe knife if the iris is caught and to reinsert a knife with a dull rounded tip. The tip of the knife is carried across the anterior chamber in the region of the angle until the point of counterpuncture is reached. The section is then completed in the regular manner. In a number of cases they have completed the section, using Castroviejo's corneal scissors. They prefer the use of a dull-tipped knife, since its use permits the sectioning of a conjunctival flap.

P. R. McDONALD.

Physiology

VISUAL PURPLE AND THE PHOTOPIC LUMINOSITY CURVE. H. J. A. DARTNALL, Brit. J. Ophth. **32:** 793 (Nov.) 1948.

The present article is concerned with the quantitative consideration of the present hypothesis that visual purple mediates the luminosity sensations of both scotopic and photopic vision and offers a *prima facie* explanation of the reduced sensitivity of photopic vision and of the Purkinje shift associated with light adaptation. Two main assumptions are made in developing the hypothesis. The first of these is that the production of visual purple from its precursors is a rapid process as compared with regeneration from its photoproducts; the second, that the influence of absorption by the photoproducts on the light absorbed by visual purple is equal to that obtaining in a homogenous mixture of the substances. It is shown that the effect of the accumulation of photoproducts (indicator yellow) in a retina exposed to light is to move the position of maximum light absorption by visual purple toward the longer wavelengths. This process is not indefinitely prolonged. As the amount of indicator yellow accumulates the light absorbed curve of visual purple rapidly approximates to a limiting position having a maximum at about 550 millimicrons. When this limiting curve is corrected for absorption by the ocular media and by the macular pigment, the resulting curve closely approximates the photopic luminosity curve. In addition to accounting for the Purkinje shift in a quantitative manner, the hypothesis provides a basis for the explanation of a number of other visual phenomena, notably the reduced sensitivity of photopic vision and the dependence of the rate of dark adaptation on the previous light history of the retina.

W. ZENTMAYER.

Refraction and Accommodation

THE FOGGING METHOD OF REFRACTION. J. M. O'BRIEN and R. E. BANNON, Am. J. Ophth. **31:** 1453 (Nov.) 1948.

O'Brien and Bannon find from refraction of 500 patients that there is agreement in a large percentage of cases between the cycloplegic and the fogging method of refraction. They feel that the capable refractionist should be familiar with the technic of fogging and the limitations of its use, as its efficacy and ease make it a valuable office procedure.

W. S. REESE.

BINOCULAR REFRACTION. P. W. MILES, Am. J. Ophth. **31:** 1460 (Nov.) 1948.

Miles considers binocular refraction a valuable refinement which permits more exact balance in the sphere between the two eyes and more exact determination of the astigmatic axis in the position of action. Binocular refraction is not useful in the absence of fusion and is less efficient when one eye is inferior to the other. W. S. REESE.

DATA CONCERNING THE HEREDITY OF ASTIGMATISM. I. BIRO, Ophthalmologica **115:** 156 (March) 1948.

The author examined 31 members of three generations of one family and found astigmatism to be of irregular dominance. He concludes that not only hypermetropia, myopia and astigmatism are hereditary, a fact which has long been known, but that their degree and axis are also inherited. H. P. KIRBER.

Retina and Optic Nerve

A STUDY OF THE ANGLE OF BIFURCATION OF RETINAL VESSELS. C. W. WASMUND, Am. J. Ophth. **31:** 12 (Jan.) 1948.

Wasmund used Bedell's fundus photographs in a study of the angle of bifurcation of normal and arteriosclerotic retinal arteries. He found the average angle 70 degrees in normal and 82 degrees in arteriosclerotic fundi, this finding being contrary to the generally accepted statements in the literature. W. S. REESE.

BLOOD SUPPLY OF THE OPTIC NERVE AND ITS CLINICAL SIGNIFICANCE. D. VAIL, Am. J. Ophth. **31:** 1 (Jan.) 1948.

Vail reviews the gross anatomy of the optic nerve and chiasm, the relations of the nerve, the circulation of the spinal fluid and blood supply. He discusses these aspects from the standpoint of their clinical significance. W. S. REESE.

FATTY EMBOLISM OF THE RETINAL ARTERY FOUND IN EYES AFTER ENUCLEATION AND ORBITAL EXENTERATION. A. LOEWENSTEIN and J. FOSTER, Brit. J. Ophth. **32:** 819 (Nov.) 1948.

While studying the retina with the slit lamp after equatorial opening of the excised eye, the authors observed, on 4 occasions, that the central artery was partly filled with fat. In the first case excision was for a malignant melanoma of the choroid in the macular area; in the second, for a malignant melanoma of the limbus, and in the third, for a perforating injury of the eyeball; in the fourth an exenteration of the orbit had been done for malignant melanoma. The embolus was more or less fluid and consisted of a fine fatty emulsion, which stained shining red with scarlet red. The fatty content of the central artery is assumed to have been aspirated from the orbital fat and emulsified by the blood. Fatty embolism of the central artery with white silvery retinal patches and superficial hemorrhages is relatively frequent with fractures of the long bones and is probably the cause of Purtscher's traumatic retinal

angiopathy. The proved fine emulsion of the fat in these 4 cases may explain the as yet inexplicable passage of fat through the pulmonary capillaries.

W. ZENTMAYER.

INTERSTITIAL OPTIC NEURITIS FOLLOWING A FURUNCLE OF THE NASAL VESTIBULE. I. TETZU, N. BLATT and J. SILVIAN, Arch. d'opht. **8:** 264, 1948.

The authors describe a case of a man aged 55 in whom an optic atrophy developed after a furuncle of the nose. This man was treated with large doses of sulfonamide drugs and penicillin. They discuss the etiologic development of the complications which may arise from infections about the nose involving the eye and orbit. The literature is reviewed. They point out that not only many orbital and cavernous sinus complications arise but that severe iridocyclitis and thrombosis of the central retinal vein and panophthalmitis can also occur. They believe that if the patient is undergoing antisyphilitic treatment this treatment should be stopped until the acute phase has subsided, since arsenic, bismuth and mercury are especially harmful to the optic nerve. Although a number of authors are cited, no bibliography is submitted.

S. B. MARLOW.

Therapeutics

AUREOMYCIN IN OCULAR INFECTIONS. A. E. BRALEY and M. SANDERS, J. A. M. A. **138:** 426 (Oct. 9) 1948.

Aureomycin borate in 0.5 to 1 per cent solution is nonirritating to the inflamed conjunctiva and only slightly irritating to the noninflamed conjunctiva. Aureomycin borate is effective in 0.5 per cent concentration in the treatment of staphylococci and pneumococcic infections, influenza and inclusion blennorrhea. The antibiotic appears to be effective in cases of rodent (Mooren's) ulcer and of atypical rodent ulcer of unknown cause. Aureomycin has some effect in epidemic keratoconjunctivitis, provided treatment is started before the fourth day of the disease. Aureomycin may be of value in dendritic keratitis. Aureomycin is a valuable addition to the armamentarium of antibiotics.

J. A. M. A. (W. ZENTMAYER.)

Trachoma

ON GENESIS AND OPERATION OF THE CICATRICIAL (TRACHOMATOUS) ENTROPION OF THE UPPER LID. A. KETTESY, Brit. J. Ophth. **32:** 419 (July) 1948.

Kettesy describes the genesis of entropion of the upper lid, the result of trachoma, and the operation he has devised to correct the deformity of the lid. The upper lid is everted by Liebermann sutures. The tarsus is divided completely in its thickness and length by an incision in the scar line of the sulcus subtarsalis. Three mattress sutures are inserted into the conjunctival margin of the section, taking up some tarsal tissue. To facilitate the turning out of the marginal tarsal strip, an incision is made the full length of the strip without buttonholing the skin. The mattress sutures are brought out through the marginal tarsal strip. After loosely knitting the sutures, the diverg-

ing ends are brought horizontally through the skin of the lid 10 to 12 mm. higher and knotted. This prevents tilting of the new intermarginal surface and secures an overcorrection.

The article is illustrated to show the steps of the operation.

W. ZENTMAYER.

Tumors

A CASE OF PIGMENTED LEIOMYOMA OF THE IRIS. N. FLEMING, Brit. J. Ophth. **32:** 885 (Dec.) 1948.

Fleming reports a case of a tumor involving apparently the whole breadth of the iris and extending over the lower and inner third of its circumference. The growth was removed by iridectomy. The pathologic diagnosis was leiomyoma of the iris with included pigment granules. The tumor had a uniform structure throughout. It was composed of spindle cells with spindle nuclei and moderately long cytoplasmic bodies. The arrangement of the cells was that commonly seen in neurofibromas, with much pigment throughout the tumor. Some of the pigment is present in a few of the cells, so that it may seem justifiable to regard the tumor as a melanotic neuroectodermal leiomyoma. In considering similar cases in the literature, Fleming states the belief that this group should not be classified offhand as leiomyoma of neuroectodermal muscle but that the point should be kept open as to whether such growths do not present characteristics that make this classification as leiomyoma as anomalous as that of the neuroectodermal musculature from which they appear to be derived.

W. ZENTMAYER.

Uvea

USE OF IMMUNE GLOBULIN IN THE TREATMENT OF UVEITIS. B. KRONENBERG, Am. J. Ophth. **31:** 1271 (Oct.) 1948.

Kronenberg gives a preliminary report of the use of immune globulin in treatment of acute forms of uveitis. In a number of cases it appeared to help in clearing up a severe uveitis which did not respond to the usual therapy.

W. S. REESE.

UVEOPIGMENTARY SENSITIZATION. H. H. JOY, Am. J. Ophth. **31:** 1581 (Dec.) 1948.

Joy discusses sympathetic ophthalmia, as well as the Vogt-Koyanagi syndrome and Harada's disease, from the standpoint of allergic response to uveal pigment. He feels that further proof must be presented to prove that the latter conditions are due to uveal pigment allergy.

W. S. REESE.

ATROPHIA GYRATA CHOROIDEAE ET RETINAE. J. SAEB, Brit. J. Ophth. **32:** 824 (Nov.) 1948.

The disease was demonstrated in 4 brothers but in neither their ascendants nor their descendants. There was a uniform clinical picture, the variations being attributable to the progress of the disease. It is reasonable to believe that the development of the condition would result in total atrophy of the choroid and retina, producing a picture resembling that of choroideremia. Nothing has been found to justify the continued classification of atrophia gyrata and choroideremia as

two distinct conditions, doing away with the concept that the former is an acquired, progressive degeneration (atrophy) and the latter a chorioretinal defect or malformation. Colored plates well illustrate the condition in the 4 cases. W. ZENTMAYER.

CHRONIC IRIDOCYCLITIS. A. LUND, Acta ophth. **22:** 176, 1944.

The treatment for chronic iridocyclitis given in the Finsen Institute is based on the assumption that the lesion is tuberculous and consists principally in a protracted series of carbon arc light baths together with injections of human tubercle bacillus protein. The author reviews a series of 88 patients, 30 male and 58 female, representing 151 affected eyes. These patients were followed closely for several years. In most patients the lesion made its appearance at the age of 20 to 30. The morbidity rate for women was also increased at about the age of 50. The duration of active inflammation, exclusive of relapses, averaged fourteen and one-half months but depended to a great extent on the age of the patient at the onset of illness: thirty-nine months for patients under 20 years and seven months for patients over 50 years of age. The duration of illness is the same for patients with positive and for patients with negative reactions to the Mantoux test. Of the 151 affected eyes, the inflammation became quiescent in 136, 56 of which subsequently had relapses. On the whole the relapses ran a mild course.

Of the total number of eyes, 63 per cent were left with good reading vision, and an additional 23 per cent had orientating vision. Operation for cataract was performed on 9 eyes. A severe relapse occurred in only 1 of these 9 eyes, while 5 had good reading vision and the rest orientating vision. In no case was the operation done until the eye had been quiescent at least a year.

One-half the patients presented roentgenographic changes in the lungs—about twice the average incidence. This, together with the favorable outcome of the treatment, is thought to lend support to the assumption of the tuberculous origin of iridocyclitis. O. P. PERKINS.

HYPERPLASIA OF THE IRIS. L. BELIKOVA, Vestnik oftal. **25:** 35, 1946.

A young soldier had impaired vision in the right eye due to chorioretinitis following trauma in childhood. Examination with slit lamp revealed two arches of trabecular tissue with holes about the pupillary region in each eye; these trabeculae had the structure of the normal stroma of the iris. The pupillary reaction was normal, and the case is reported because of this rare congenital anomaly. O. SITCHEVSKA.

Vision

EFFECT OF EXPOSURE TO SUNLIGHT ON NIGHT VISION. S. HECHT, C. D. HENDLEY, S. ROSS and P. N. RICHMOND, Am. J. Ophth. **31:** 1573 (Dec.) 1948.

Hecht and his co-workers found that exposures to ordinary sunlight produced temporary and cumulative effects on night vision. They strongly recommend sunglasses transmitting 10 per cent or less of visible light for all persons who work in bright sunlight during the day and are then expected to perform critical night duties.

W. S. REESE.

Book Reviews

Text-Book of Ophthalmology. Vol. IV. By Sir W. Stewart Duke-Elder. Price, $20. St. Louis: C. V. Mosby Company, 1949.

The long anticipated fourth volume of the "Text-Book of Ophthalmology" by Sir Stewart Duke-Elder has at last appeared with an apology for keeping us waiting because the author was for six years concerned with "matters outside the library." This volume is well worth the wait. It continues the now almost legendary influence the three previous volumes have had on ophthalmology in the English-speaking world.

If one reflects back to the period prior to the publication of volume I of this monumental work, it will be recalled that no ophthalmologist could be really well informed who did not have a reading knowledge of at least German and French. In order to cover the literature on any ophthalmologic subject, either in the basic sciences or in clinical subjects, one had to read the material in the original publication, and it was a most lamentable fact that this was seldom in the English language. With the appearance of Sir Stewart's text ophthalmologists were afforded for the first time a complete coverage of the world's ophthalmologic literature in English. In addition to being an excellent compilation of the literature, the material was assorted and evaluated with an amazingly astute comprehension of what was wheat and what was chaff.

In each new volume as it has appeared the material covered was exhaustively and authoritatively treated, so that most of us readily came to accept it as the last word on the subject. In more than one clinic in this country the three volumes are affectionately referred to as the "Bible," and without any loss of reverence for either work. There can be no doubt that these four volumes have revolutionized the teaching of ophthalmology in this country, and our debt to their author is beyond measure.

The present volume is entitled "The Neurology of Vision: Motor and Optical Anomalies." It is as comprehensive and beautifully executed as the previous volumes. The section on neurology starts with disorders of the visual pathways and their associated dysfunctions. This is followed by anomalies of the pupillary pathways, and, finally, the disturbances of the oculomotor apparatus are dealt with, including comitant squint and its associated sensory phenomena. In this systematic anatomic progression, the author covers the whole field of organic and functional pathology of the central nervous system as it finds expression in the eye. As in the previous volumes, the coverage of the world's literature seems to be complete, and the bibliography put at the end of each section saves considerable time when one wishes to refer to the original articles.

The last section of this volume covers the optical anomalies of the eye. Since the author has recently published the fifth edition of his "Practice of Refraction," this part of volume IV does not create the same excitement as the rest of the book, but not because it is of less value.

The style is the same as that which has characterized the other volumes in the set—lucid, and with a nice flow of words that satisfies one's sense of rhythm—and yet it is never verbose. It would make many of our publications more pleasant reading if Sir Stewart's style could be emulated. The paper, printing and, above all, the illustrations are superb. To the author of the present volume, and to all those who have contributed to its making, American ophthalmology owes a sincere debt of gratitude.

F. H. ADLER.

Help Yourself to Better Sight. By Margaret Darst Corbett. Price, $2.50. Pp. 218. New York: Prentice-Hall, Inc., 1949.

The author was a pupil of the late William H. Bates and has been carrying out his teachings in her own Los Angeles School of Eye Education. If the results of this type of quackery were not so tragic, the book could be highly amusing. Chapter 9, for example, gives a summary of daily drills for relaxation of the eyes, starting on page 42 with the following instructions:

2. Yawn wide like a hippopotamus, dropping your chin, taking your head away from it and coming back to get it again. This loosens the lungs for deep breathing. There is nothing more effective than a yawn. Watch a dog or baby to perfect your skill.

3. Wiggle like a fish. Visualize the vertebral activity of a fish as it swims through the water. Try to imitate it by wiggling your own spine from the base of the skull down to the very last vertebra. Now your body is free.

In addition to such exercises as blinking and massaging the eyeballs, the author suggests brow wangling, which, she says, divorces the brows from the lid action.

FRANCIS H. ADLER, M.D.

How to Become a Doctor. By George R. Moon, A.B., M.A. Price, $2. Pp. 131. Philadelphia: The Blakiston Company, 1949.

This book fills the need for some authentic instruction to students in college who are contemplating going into medicine or one of the allied professions, such as dentistry, pharmacy or occupational therapy. A list of the approved medical schools in the United States for 1948 is given together with their requirements for admission. There is a chapter on advice in selecting a medical school, as well as chapters on how to apply for admission and several chapters on the problems with which the medical student will find himself confronted. The book is highly recommended for any student considering entering the medical profession.

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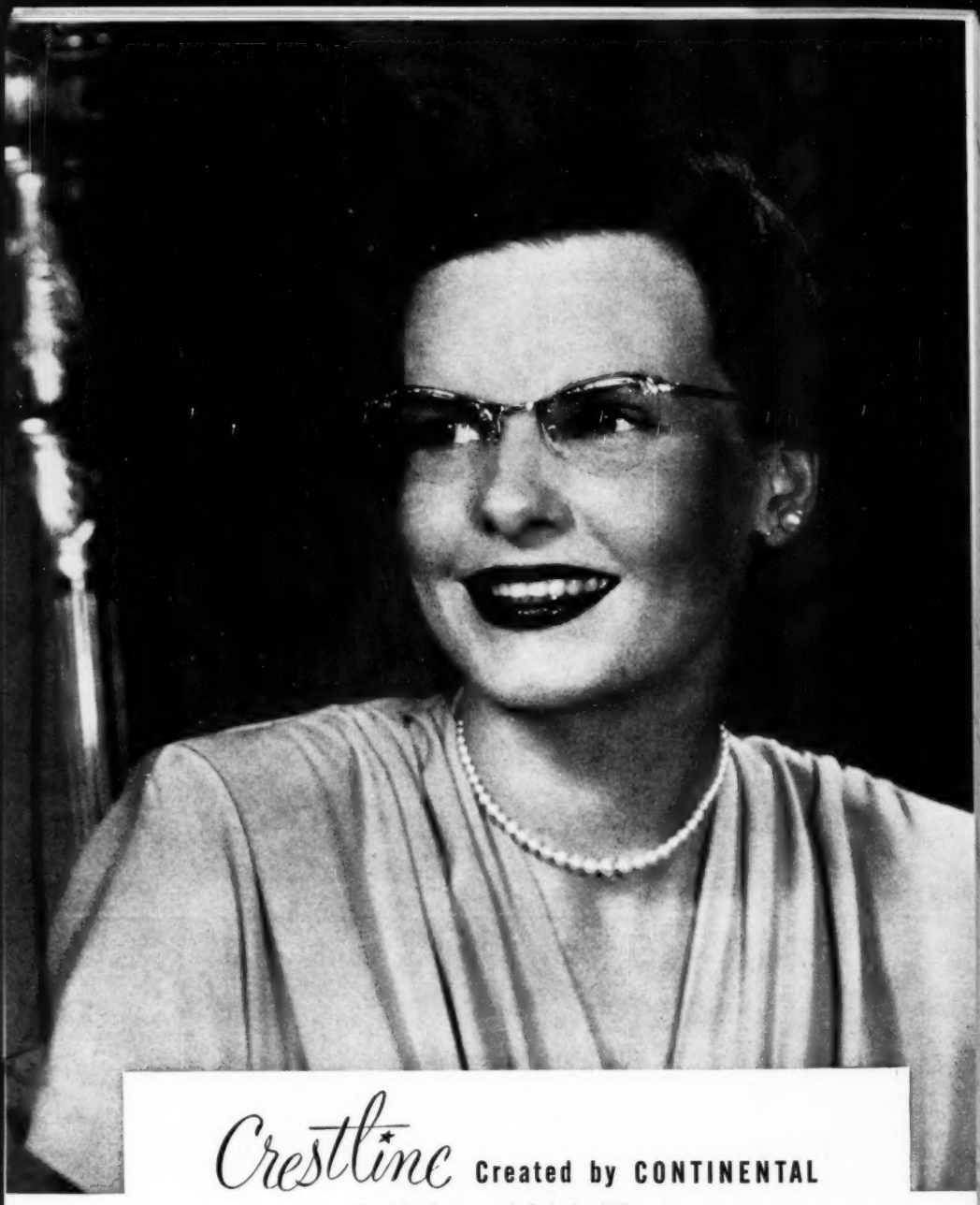

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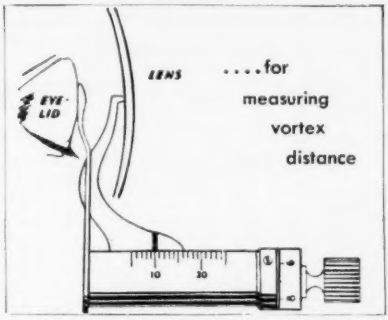

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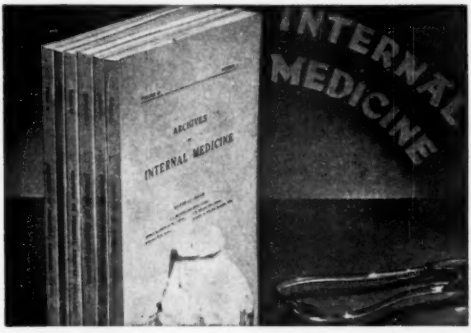

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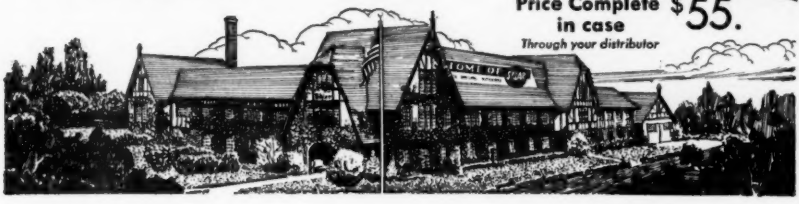

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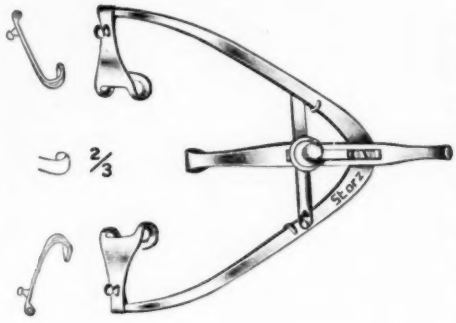

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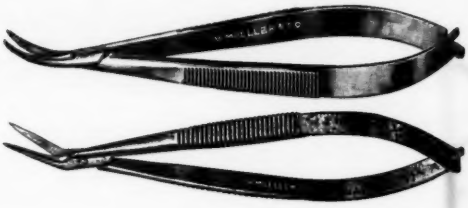

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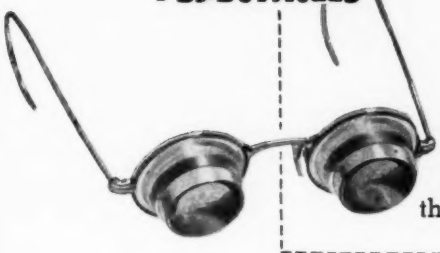

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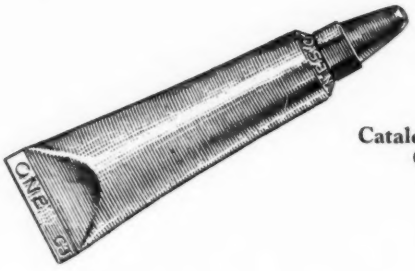

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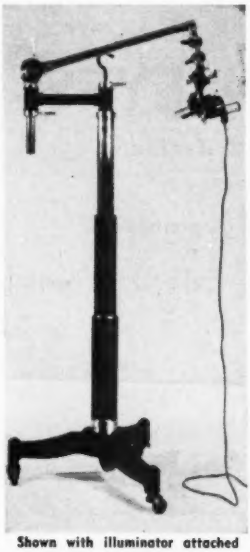

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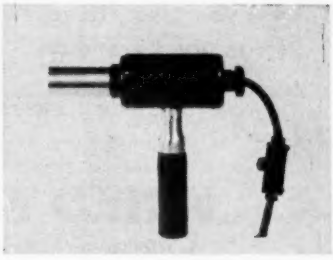

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